THE PRACTICE OF INFECTIOUS DISEASE

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THE PRACTICE OF INFECTIOUS DISEASE

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PREFACE

This book is written for the practitioner of medicine, many of whose patients present themselves to him with problems of an infectious nature. Despite the availability of potent antimicrobial agents, it is a striking fact that the incidence of many of the common infections has not been significantly reduced. In addition, "new" diseases, mostly due to viruses, are being reported with considerable frequency. Superimposed on the problems of the frequency of "old" diseases and the appearance of "new" ones are the pressing necessity for specific diagnosis, the proper selection and application of chemotherapy, and the fact that the administration of any antibiotic agent is not without danger. It is obvious, therefore, that the field of infectious disease is expanding and not contracting, and that as one group of difficulties becomes manageable, it is replaced by others which are diagnostically and therapeutically perplexing.

When a physician sees a patient with an infectious disease, his attention is usually first directed, on the basis of the history and physical examination, to a particular organ system and not to a specific etiologic agent. This is so because most tissues respond to injury in a limited number of ways and identical syndromes are frequently produced by widely different organisms. Thus, for example, the physician's first impression is of disease of the lungs rather than streptococcal pneumonia, or infection of the nervous system rather than pneumococcal meningitis The etiology of an infection is usually determined only after special studies have been carried out, but these are practically always selected on the basis of the location of the disease process. For these reasons, the infections discussed in this book have been grouped

together in relation to the organs in which they occur, rather than on the basis of the microorganisms which cause them. It is the hope of the writer that this will, in some measure, lighten the burden of differential diagnosis and facilitate the intelligent selection of treatment.

Limitation of space has precluded the inclusion of descriptions of all of the infectious diseases of man. The writer has discussed, therefore, only those which are observed most frequently in the United States and Europe, even some of these have had to be omitted. "Tropical" diseases, even such common ones as malaria, cholera, and most of the worm infestations have not been described even though they occur at times in the Temperate zone.

None of the statements in this book have been documented by bibliographical references. They are nevertheless the distillate of the observations of a very large number of clinicians and investigators to whom the writer is greatly indebted. He also wishes to express his gratitude to his teachers, medical colleagues, and to the many patients from whom he has learned much of what he has committed to the pages of this book.

Part of this book was written while the author was Associate Professor of Medicine at the Boston University School of Medicine and Chief of the Department of Infectious Diseases of the Massachusetts Memorial Hospitals in Boston, Massachusetts.

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CONTENTS

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CHAPTER I

PRINCIPLES OF THE DIAGNOSIS OF INFECTION

Twenty years ago the establishment of a specific etiologic diagnosis in many infections was of little or no help to the physician or his patient. For example, nothing was gained from the differentiation of pneumococcal, tuberculous, or staphylococcal meningitis because effective therapy was not available, and death was the outcome in all but a rare case. With the present availability of potent and highly effective antimicrobial drugs, however, it has now become of paramount importance to establish an exact etiologic diagnosis as rapidly as possible, so that the proper chemotherapeutic agent can be intelligently selected and treatment instituted. A number of approaches, both clinical and laboratory, are useful in the diagnosis of infectious disease.

Clinical Features of a Disease

In the present enthusiasm for laboratory studies, there is a tendency to overlook the fact that the clinical pictures of some infectious diseases are sufficiently characteristic to suggest their etiologic background. For example, the patient who suddenly develops a chill followed by fever, pleuritic pain, a cough productive of bloody sputum, and abnormal physical findings over one of the lower lobes of the lung, in all probability is suffering from pneumococcal pneumonia. While other types of pneumonitis may have the same onset, it is commonest with pulmonary infection due to the pneumococcus. The patient with stiff neck and back, fever and chills, changes in sensorium, purulent spinal fluid, and

Equine encephalitis should be suspected in individuals with fever and neurologic manifestations if they have been in a vicinity in which horses are known to be suffering with this disorder. A history of contact with a known case of specific infection, streptococcal pharyngitis, measles, varicella, etc. is often sufficient to indicate the etiology of an acute febrile process. Information concerning past experience with infectious diseases may be of help in ruling out certain possibilities; for example, second attacks of the acute exanthemata, pertussis, or meningococcal meningitis are very uncommon. The ingestion of contaminated food or water suggests the possibility of any of the infections transmitted by the oral route, such as the salmonelloses, typhoid fever, bacillary dysentery, amebic colitis, infectious hepatitis, and trichinosis. A story of contact with animals often directs the attention of the physician to specific possibilities. The patient with a severe "virus" pneumonia should be questioned concerning exposure to birds. The appearance of a "pimple" on the skin of a man whose work involves the handling of skin, furs, or hair is suggestive of anthrax. The abbatoir worker with an undefined pneumonitis may have Q fever. The farmer, veterinarian, or meat packer with fever and weakness, but without localizing signs, should be investigated for brucellosis. Inquiry into previous immunizations may aid in ruling out certain disease states. A recently acquired cowpox vaccination scar, for example, makes the likelihood of smallpox in an individual with fever and a diffuse vesicular eruption remote.

Information Derived from Various Stained Preparations

The difficulties associated with attempts to establish specific diagnoses by microbiological methods when patients are seen at home or in an office cannot be belittled. There are, however, certain practical approaches to this problem which give the physician information of great help in establishing a strongly presumptive or even exact etiologic diag-

a petechial skin eruption usually has meningococcal meningitis. In these two diseases, as well as in others, the nature of the infectious agent can be suspected on clinical grounds, although it must always be confirmed by laboratory study. Initial therapy may be specific before the causative organisms have been isolated and identified in such instances.

With some of the infectious diseases, however, the syndromes which develop are quite identical, regardless of the nature of the responsible agent. For example, one cannot differentiate clinically the diarrhea produced by the typhoid bacillus, salmonellae, dysentery bacillus, or even viruses. The acute bacterial meningitides in which skin eruptions do not appear also cannot be distinguished, with some exceptions, on a clinical basis alone, because they are all accompanied by signs of meningeal irritation and identical spinal fluid changes. However, the mode of onset of some types of meningitis suggests the etiologic agent. Thus, meningeal infection secondary to disease of the ears or paranasal sinuses is usually due to the pneumococcus, staphylococcus, or streptococcus, and rarely, if ever, the meningococcus. When meningitis follows a pneumonia, it is very often due to the pneumococcus in adults, and *H. influenzae* in children.

Epidemiologic Information

The epidemiologic background of an undiagnosed infection is often very helpful in suggesting its etiology. For example, the season of the year is significant in relation to some specific diseases. Thus, non-bacterial infections of the nervous system occurring in the summer are apt to be poliomyelitis, equine encephalitis, or due to Coxsackie viruses. Information concerning the types of disease present in the community in which a patient resides may be very important. The person with chills and fever, but no localizing signs, who has recently lived in a part of the world in which malaria is endemic should be studied for this disease.

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nosis. A very useful procedure in this regard is the microscopic examination of exudates, discharges, and body fluids by means of properly stained smears. For example, a Gram-stained throat smear obtained from a patient with acute pharyngitis may immediately demonstrate the predominant and probably causative organism. Stained preparations of exudate from abscesses, purulent conjunctivitis, or suppurative otitis media, or from sputum in pneumonia often reveal the responsible bacteria. In some instances, the morphology and reaction to the Gram-stain of an organism are sufficiently characteristic to allow its exact identification; this is often the case in gas gangrene, tetanus, anthrax, and meningococcal, pneumococcal, or staphylococcal infections. Wright-stained blood smears may rapidly clear the confusion of an obscure fever by revealing the presence of malarial parasites. Gram-stains of centrifuged spinal fluid in purulent meningitis frequently disclose the responsible bacteria and allow the initiation of antimicrobial therapy very early in the course of the disease, obviating, in many situations, the necessity of administering treatment empirically. In cases of suspected urinary tract infection, the sediment of urine obtained by the "clean catch" method should always be gram-stained. Such a study yields two valuable pieces of information: (1) The demonstration of organisms in the smear usually indicates the presence of infection, rather than contamination, and (2) the nature of the bacteria—gram-positive or negative, rod or coccus—is revealed. The importance of examination of sputum by means of acid-fast stains when tuberculosis of the lungs is being considered cannot be overemphasized; false-positive results are present, however, in about one per cent of such studies. Properly stained smears of material obtained by aspiration of bone marrow or liver not infrequently establish the diagnosis of miliary tuberculosis some time before clinical or cultural studies, or animal inoculations prove its presence. In some diseases, stained smears are of no value. A good example is

the enteric bacillary infections in which it is impossible to distinguish, on the basis of morphology and staining reaction, the typhoid bacillus, the Salmonellae, and the dysentery bacilli from the gram-negative organisms (*E. coli, Proteus, Ps. pyocyaneus, A. aerogenes*) normally present in the bowel. It must also be stressed that failure to demonstrate bacteria in stained preparations does not necessarily rule out their implication in an infectious process.

Specific Microbiologic Studies

It is usually impossible for the physician practicing primarily outside the hospital to carry out the microbiologic technics necessary to specifically identify disease-producing organisms. This requires considerable equipment and specially trained personnel, and is best done in the hospital, municipal, or state laboratory. Despite the fact that he himself does not carry out the procedures involved in this type of study, the practitioner of medicine must be aware of the situations in which cultures are necessary, the materials which should be cultured, and the methods of obtaining and transmitting them to the bacteriology laboratory.

Blood cultures should be drawn, whenever possible, in any patient with fever. Although bacteremia is detected most often when the temperature is high, organisms may be present in the blood in cases with a low-grade febrile response. The best time to make a blood culture is at the point where the temperature is just beginning to rise or during a shaking chill. A minimum 10 ml. of blood should be withdrawn under the strictest aseptic precautions and inoculated into about 75 to 100 ml of broth. In addition, it is well to incorporate 1 ml. of blood into an agar pour-plate, in order to estimate the degree of bacteremia and to rule out the possibility of contamination, if growth occurs in the liquid medium The bacteriologist should be informed of the clinical possibilities being considered, so that proper bacteriologic technics can be carried out.

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contamination from the skin. Beta-hemolytic streptococci may at times be isolated in a throat culture of a patient who has viral pharyngitis. Salmonella or dysentery bacilli may be demonstrated in the feces of patients with diarrhea, but may merely represent the carrier state. Data obtained from bacteriological studies alone, therefore, are of little diagnostic significance; they must always be correlated with the clinical findings, before they can be accepted as indicating the etiology of an infection. That this is so is further illustrated by the occasional case in which "non-pathogenic" organisms produce serious disease. Thus, *B. subtilis* rarely has induced a purulent meningitis, *Alcaligenes fecalis* has been responsible for bacteremia, and *L. acidophilus* has been the causative agent in a case of endocarditis.

Bacteriological Statistics

"Bacteriological statistics" are data concerning the frequency of infection of certain organ systems by specific microorganisms. Such information may be of great help in making an "intelligent guess" of the etiology of an infectious process. For example, infections of the urinary tract most frequently involve *E. coli, Ps. pyocyanea, Proteus, H. influenzae, Staph. aureus,* and streptococci. Acute purulent otitis media in adults is most often due to *Staph. aureus,* pneumococci, or beta-hemolytic streptococci; in children, on the other hand, *H. influenzae* is a very common cause of this disease. *D. pneumoniae* is responsible for many cases of pneumonia in adults; *H. influenzae* produces primary infection of the lungs only very rarely in this age group. The organisms isolated from chronic otitis media are gram-negative rods such as *Proteus* and *Ps. pyocyaneus* Acute osteomyelitis is produced in the bulk of instances by *Staphylococcus aureus. Strep. viridans* is the causative agent in 95 per cent of the subacute bacterial endocarditides. These are just a few examples of the application of "bacteriologic

Any material which can be obtained from an infected area should be cultured; this includes spinal fluid, urine, sputum, exudate from localized areas of infection, stool, bone marrow, blood, and throat secretions. Although it may not always be possible to culture the pharynx of all individuals with "sore throat," such study must never be omitted when a membranous pharyngitis is present because, without it, the diagnosis of diphtheria cannot be confirmed. In instances in which bacterial infections are strongly suspected but organisms fail to grow, the possibility of anaerobic, mycotic, or acid fast disease must be seriously considered and appropriate cultures made.

Most hospitals are at present not equipped with either the means or the personnel for the isolation and culture of viruses. Materials requiring this kind of study must be sent to special laboratories, many of which are conducted by governmental public health agencies. For the practicing physician, clinical findings are of much greater diagnostic help in the early phase of many viral infections than attempts at specific identification of the infectious agents. Some of the diseases in which the virus can be isolated with relative ease are mumps (saliva), influenza (throat washings), viral diarrheas (stool), Coxsackie disease (stool), and poliomyelitis (stool).

Animal inoculation is necessary for establishing the presence of some infections. This is of help in tuberculosis, leptospirosis, anthrax, and other diseases which are discussed in detail in other chapters of this book.

The isolation of a pathogenic organism does not always establish its causal relationship to an infectious process. For example, the recovery of staphylococci from the pharynx *does not prove that they are responsible for a sore throat* because about 60 per cent of normal people harbor this organism in the upper respiratory tract. A single positive blood culture containing staphylococci does not necessarily indicate the presence of bacteremia but may be due to

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There are a number of non-specific serologic tests which are nevertheless helpful in diagnosis of particular infections. The reactions, in these instances, do not involve the use of the infectious agent responsible for the disease. Examples of such tests are the Wasserman and Kahn type reactions in syphilis, cold agglutination in "viral" pneumonia, and heterophile agglutination in infectious mononucleosis.

Pathological Study

In some cases, the etiology of an infectious disease cannot be established by any of the methods described above. In such instances, anatomical study of the involved tissues or of organs in which metastatic areas of infection become established may be the only way in which a specific diagnosis can be made. The nature of the cellular reaction and the demonstration of organisms by staining or culture in biopsy specimens are very helpful, for example, in detecting the presence of miliary tuberculosis (bone marrow, liver), chicken pox, diffuse herpes simplex, herpes zoster, or widespread vaccinia (skin), asymptomatic pyelonephritis (kidney), or idiopathic pleural effusion.

statistics." On the basis of such information it is possible, in a number of instances, to make a presumptive etiologic diagnosis and to start chemotherapy before specific data obtained by more definitive microbiological procedures become available.

Serological Studies

Serological studies are, for the most part, helpful in indicating the etiology of an infection only retrospectively. In some instances, however, they are valuable in the acute phase of a disease. The identity of meningococci, *H. influenzae*, pneumococci, and the Friedlander bacillus in spinal fluid or sputum can be quickly established, for example, by mixing a small quantity of these fluids with specific antiserum; this results in capsular swelling which is specifically diagnostic. Skin testing may be employed in some diseases for rapid diagnosis; this is useful in suspected instances of tuberculosis, trichinosis, histoplasmosis, cat scratch disease, lymphogranuloma venereum, and coccidiomycosis, for example. A positive reaction may indicate only past experience with one of these infections, and bear no relationship to the active process being studied. A negative test has greater validity in ruling out, with uncommon exception, the presence of a specific disorder. Age often plays a role in the interpretation of skin reactions. Thus, a positive tuberculin test in an adult is without significance in indicating active tuberculosis; in a child, on the other hand, it usually signifies the presence of active disease. If a skin test has been known to be negative and becomes positive during the course of an infection, it usually establishes specific diagnosis.

With the above exceptions, serologic tests are useful mainly in making diagnoses after a disease has been present for some time, or recovery has occurred. In typhoid fever and brucellosis, the specific agglutination titers rise to significant levels while infection is still active. In other infec-

tious diseases, mumps, influenza, psittacosis, viral encephalitides, bacillary dysentery, streptococcal and pneumococcal infections and leptospirosis, for example, serological studies usually are not positive until the convalescent phase. The specific methods employed in various diseases are indicated in the chapters dealing with the individual disorders. It must be stressed that the results of a single serologic test may have no diagnostic significance, even if the titer is elevated, because it may merely reflect previous experience with an organism or immunization. For this reason it is necessary, whenever possible, to obtain one serum in the acute stage of infection and another in the late phase or during convalescence. The demonstration of a minimum of a four-fold increase in specific antibody level is usually diagnostic.

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Findings Suggestive But Not Diagnostic of Infection

There are a number of findings present in patients with infectious disease which are suggestive but not diagnostic of infection because they may also occur in other disorders. These include fever, changes in white blood count, chills, generalized malaise, elevated sedimentation rate, or positive C-reactive protein tests.

Fever does not always mean infection. It may be of high degree in non-infectious processes. Chills and generalized malaise also occur in diseases which are not due to invasion by living organisms.

White blood counts may be of no help in distinguishing infections from non-infectious disorders or in differentiating the various types of infection. While, as a rule, leucocytosis appears in diseases due to bacteria, and leukopenia is found in those due to viruses, there are a great many exceptions. In some virus infections, the white blood count and relative number of neutrophiles are increased. In severe bacterial infections, on the other hand, it is not rare for leukopenia and granulopenia to be present; in many of these a sharp increase in the total number of white blood cells and in young polymorphonuclear cells follows the institution of effective therapy and indicates a favorable prognosis.

Elevation of the sedimentation rate is not diagnostic of infection; it is not uncommonly normal in the early stages of some infectious processes and may be increased in myocardial infarction, various neoplastic diseases, and other disorders. The same is true of the level of C-reactive protein in the blood. Both of these tests have their greatest value in following the course of a disease. Determinations of C-reactive protein are of greater significance in this regard than the erythrocyte sedimentation rate.

CHAPTER II

PRINCIPLES OF TREATMENT OF INFECTION

Non-Specific Therapeutic Measures

Bed Rest. Patients with moderate to servere infectious diseases should be put to bed, particularly during the early stages of their illness. Very often the patient seeks complete rest, even without the advice of the physician. The load imposed on metabolism, the protein-wasting, and discomfort in general which result from the fever and other effects of infection are reduced and kept at a minimum by bed rest. This should not be prolonged, however, beyond one or two days after defervescence has been established, especially in individuals over the age of 40 years, except in instances where complications, particularly those involving the cardiovascular system, appear. There are four important undesirable effects of prolonged bed rest: (a) General weakening resulting from physical inactivity may prolong the period of convalescence and delay return to normal physical activity. (b) One of the most dangerous consequences is phlebothrombosis of the legs resulting in pulmonary infarction. While this is primarily a problem in older individuals, it also occurs, although less commonly, in young ones. It is best prevented by early mobilization but, when this is not feasible, the use of elastic stockings properly fitted and covering the legs from the inferior border of the patella to the middle of the foot reduces appreciably the risk of venous thrombosis. (c) Immobilization for long periods of

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Elevation of the sedimentation rate is not diagnostic of infection; it is not uncommonly normal in the early stages of some infectious processes and may be increased in myocardial infarcation, various neoplastic diseases, and other disorders. The same is true of the level of C-reactive protein in the blood. Both of these tests have their greatest value in following the course of a disease. Determinations of C-reactive protein are of greater significance in this regard than the erythrocyte sedimentation rate.

protein diets are especially indicated unless marked depression of hepatic function is present in which case they increase the risk of ammonia poisoning. Increased protein ingestion may be necessary for the proper formation and activity of antibodies. There are no anti-infective vitamins, and the use of such agents to prevent or treat infections is not indicated. The hypermetabolic state associated with fever, however, increases the utilization of vitamins. Decrease in production of vitamin K results from changes in the bacterial flora of the intestinal tract produced by the oral administration of "broad-spectrum" antibiotics. Patients with serious or prolonged infections may develop various vitamin deficiencies for these reasons.

Water and Electrolyte Balance. Maintenance of fluid and electrolyte balance is essential in all infectious diseases regardless of their etiology or response to treatment with specific drugs and is more important in determining the outcome, in some instances, than the use of antibiotics. Infections in which high fever, severe sweating, diarrhea, and vomiting are present are the ones most difficult to control in this regard; this is especially true in young children in whom dehydration and acidosis often develop very rapidly. Salt losing syndromes have been observed during the course of some infectious processes—tuberculous and meningococcal meningitis and chronic pyelonephritis. Great care must be taken to maintain a normal serum potassium level, particularly when there is diarrhea or inability to take food. The generalized weakness and even electrocardiographic changes noted in some infections may be due to the insidious appearance of hypokalemia. In patients with pneumonia or other conditions in which tachypnea or hyperpnea appear, changes in the carbon dioxide content of the blood are frequent. If anorexia and diarrhea are also present, it becomes very difficult to interpret the significance of the serum CO_2 A decision can be made in such cases only by studying the pH of the urine at frequent intervals or, better

time, particularly in patients with paralyzing disorders or those whose limbs have been put in casts, results in demineralization of the bones, hypercalcemia, and stone formation in the urinary tract. This can be minimized, although often not completely prevented, by reduction in calcium intake, increasing the quantity of water ingested to maintain a low specific gravity of the urine, moving the limbs about as much as is compatible with the disease, and, as has been suggested most recently, administering moderate quantities of salicylate. (d) In elderly individuals, especially males, enforced bed rest may increase urinary bladder residual and result in cystitis or pyelonephritis or both, especially if prostatic hypertrophy is present or if catheterization has been performed.

The type and severity of the infection, the presence of cardiovascular complications, the age of the patient, and other factors should influence the physician's recommendation concerning the advisability and duration of bed rest. The possibility of the development of the complications described above must be kept in mind constantly, and all measures which might prevent their appearance or minimize their effects put into practice early.

Nutrition. For every degree Fahrenheit elevation in body temperature above normal, the metabolism requires an additional 140 calories (252 calories per degree Centigrade). Wherever possible, therefore, the caloric intake of patients with febrile diseases should be increased to a degree sufficient to correct the deficit resulting from the hypermetabolic state. Infection, regardless of its etiology, is almost always accompanied by negative nitrogen balance; the exact mechanism of this is not known, but it may be due to elevation of the temperature. Although it is frequently impossible to correct the nitrogen deficit by giving increased quantities of protein, the intake of high-protein food should be urged in patients with severe or prolonged infectious diseases. In infectious hepatitis or other infections of the liver, high

sure. The writer does not use salicylates for the reasons stated below. In certain situations, non-specific measures are often of great help. For example, the discomfort of pharyngitis can be relieved by gargles or irrigations with warm physiologic salt solution, and the severe muscle aching of poliomyelitis considerably reduced in intensity by the proper application of moist, warm packs or by changing the position of the paralyzed limbs.

Fever. The advisability of strenuous efforts to reduce fever is debatable. The discomfort associated with an elevated temperature may be relieved with analgesics without reducing the fever, the presence of which may be of importance for two reasons. (1) The degree of temperature elevation is of great aid in gauging the course of an infection and its response to therapy. (2) It has been suggested that, within certain limits, the effectiveness of many of the immunological processes of importance in recovery is directly related to the temperature at which they are operative. Rapid defervescence with antipyretic drugs may convert a flat, high temperature into a spiking one accompanied by chills which precede each sharp elevation. The writer has noted the appearance of marked hypotension on a number of occasions and death in one case when rapid defervescence from a high level has been accomplished by salicylates. It has been suggested that temperature elevations up to 105°F. are without danger, and that this represents another point at which the heat-regulating mechanism functions within physiological limits. If fever is higher than this, rubbing of the skin with warm alcohol, ice-water enemas, or wrapping the patient in cold sheets are often very effective in reducing the temperature. It is important to point out that mere patting of the skin with alcohol is usually of no avail, in fact, this may accentuate the vasoconstriction of the dermal vessels already present and increase retention of heat. The skin should be rubbed briskly until it becomes red; this indicates vasodilation and is accom-

yet, determining the pH of the serum. The administration of excessive quantities of water and sodium chloride must be avoided because of the dangers of hypervolemia and pulmonary edema. Frequent determinations of the blood sodium, chloride, potassium, carbon dioxide, and pH should be carried out in all serious infections and abnormalities corrected before they exert an unfavorable influence on the course of the disease. Determination of the hematocrit is a simple and useful method of evaluating the state of hydration; if, in the absence of bleeding or other cause for anemia, the volume of erythrocytes is falling, the possibility of overhydration must be entertained. Looseness of the skin, especially over the forehead, is suggestive of dehydration, while peripheral edema indicates excessive administration of water.

Anemia. Most severe or prolonged infections are accompanied by rapidly progressing microcytic, hypochromic anemia. This is probably due to defective utilization of iron. The oral administration of iron is usually of no help; it has been suggested that intravenous injection may be more effective. The best method of correcting the anemia of infection is blood transfusion.

Relief of Pain and Discomfort. One of the most important functions of the physician who treats infections or any other type of disease is to make the patient comfortable. Attention must be paid to establishing normal evacuation of the bowel and bladder. The skin should receive meticulous care; daily massage, bathing, and powdering not only produce comfort but, properly carried out, reduce the risk of development of bed sores. To disregard pain is to neglect the patient badly. Analgesics should be used freely, within the limits of the nature of the disease and the toxic properties of the drugs; pain must be reduced to the absolute minimum. Demerol and codeine are very useful agents for this purpose. Morphine derivatives are contraindicated in acute infections of the central nervous system with increased intracranial pres-

of soci-economic disruptions, and occupational therapy are all very helpful in the prevention and therapy of these emotional difficulties. The physician not trained in psychiatry should guard carefullly against inept probing because this may serve only to aggravate the situation and may even produce tragic results. The psychiatrist must be consulted when these problems arise.

Adrenal Steroids. The adrenal steroids have been used most often during the acute phase of severe infections and for the therapy of shock. While it has been suggested that cortisone is of value in the early stages of acute brucellosis or typhoid fever, it has been stressed that it should not be given for longer than the first few days, until defervescence has taken place. The steroids are antipyretic, a disadvantage of their use, therefore, is the abolition of fever as a gauge of the course of an infection. Under the impact of the steroids, an infectious process may be progressing while the patient's chart suggests recovery. Persistent pneumococcal and *Proteus* bacteremia have been observed in the absence of fever, when cortisone has been administered. There is considerable evidence that infectious agents are more widely *disseminated under the influence of these drugs. There is* little doubt that experimental and naturally-occurring virus infections have been made more severe than usual, and latent tuberculosis has been activated following the use of steroids. Death from overwhelming chicken pox has been described in a number of cases in which cortisone was being given for an unrelated process at the time contact was made with the agent of varicella Large doses of steroid appear to depress the antimicrobial activity of antibiotics For these reasons, the writer does *not recommend* the use of steroids in any type of infection, except in the most unusual and critical situations, until evidence has been presented that these drugs are potentially more beneficial and less harmful than they appear to be at present.

panied by a fall in temperature. A decrease of 2 to 3 degrees is sufficient. In some instances, salicylates may need to be given; if so, they should be administered in quantities which will not produce too great a degree of defervescence too rapidly. For hyperpyrexia of neurogenic origin, the use of chlorpromazine has been advised. To produce the desired effect, the drug has to be given parenterally; it may produce severe depression of blood pressure.

Shock. One of the most difficult problems in infectious disease is the treatment of the severe hypotension and the other manifestions of the shock state which may be present. The mechanism of these manifestations is unknown. For this reason, it is impossible to recommend any specific therapeutic measures. Although it has been used extensively, there is no good evidence that the administration of plasma influences favorably the shock of infection. The head down position and warm blankets may be useful. The most effective agents for the management of this condition are vasoconstricting drugs such as ephedrine, neosynephrine and norepinephrine. These are best administered intravenously and must be given as early as possible before the situation becomes irreversible. The best therapy for this type of shock is intensive chemotherapy, wherever possible. Until the infectious process responds to antibiotics, the vasoconstricting agents serve as a very helpful stopgap. In most cases, death will result unless progress of the infection is halted.

Emotional Disorders. Severe emotional disturbances, including frank psychoses, may develop during the acute or convalescent stages of a number of infections, without relation to the severity of the primary disease. They are particularly common in prolonged disorders such as tuberculosis and paralytic poliomyelitis. Proper approach to the patient by the personnel responsible for his care, encouragement but not hyperoptimism, understanding without pity, correction

of soci-economic disruptions, and occupational therapy are all very helpful in the prevention and therapy of these emotional difficulties. The physician not trained in psychiatry should guard carefullly against inept probing because this may serve only to aggravate the situation and may even produce tragic results. The psychiatrist must be consulted when these problems arise.

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SPECIFIC THERAPEUTIC MEASURES ANTIBIOTICS, SULFONAMIDES AND TUBERCULOSTATIC DRUGS

The Sulfonamides

The sulfonamide compounds have been used in clinical medicine since 1937. A number of agents of this type have been developed; a few have been found to be effective in some diseases and relatively nontoxic in man. At the present time the most widely used sulfonamides are sulfadiazine and sulfisoxazole, which are rapidly absorbed from the intestinal tract, and the relatively non-absorbable agents succinylsulfathiazole (Sulfasuxidine) and Sulfathalidine.

The sulfonamides, although employed less often today then they used to be because of the availability of potent antibiotics, are still the drugs of choice in the management of such infections as meningococcal meningitis and bacillary dysentery. They are also used in the prophylaxis of rheumatic fever and, with varying success, in urinary tract infections which have not responded to other antibacterial agents. These agents are used at times in conjunction with other antibacterial substances in the treatment of severe systemic infections. Although there is a clinical impression that an additive chemotherapeutic effect may be produced by combining a sulfonamide with an antibiotic, data from carefully controlled studies are meager.

The sulfonamide compounds at present employed for the treatment of systemic infections are readily absorbed from the gastrointestinal tract and are probably best given by the oral route to the conscious patient. Soluble sodium salts of the drugs are available for parenteral injection when administration by mouth is difficult or impossible, when intestinal absorption is poor, or when high blood levels are

required. In the treatment of meningococcal meningitis, intravenous or subcutaneous injection of the first one or two doses of sulfadiazine produces more rapid defervescence than when initial therapy is given orally. Liquid preparations made palatable by the addition of flavoring materials are useful in treating young children. For most of the infectious diseases in which the sulfonamides are of value, the duration of therapy should be no less than one week; in special instances a longer period may be necessary.

An adequate concentration of sulfonamide must be maintained in the blood and tissues to produce effective bacteriostasis. A blood level of 10 to 12 mg. per 100 ml. is sufficient in most susceptible infections. The interval between separate doses is usually 4 to 6 hours. If the drugs are given parenterally, the interval between doses is increased in order to avoid the development of excessively high plasma levels. Concentration of drug in the blood should be estimated at frequent intervals in order that the quantity administered may be adjusted properly; this is simply and accurately determined by colorimetric methods.

Most of the sulfonamide compounds are widely distributed in the body. Exceptions are succinyl-sulfathiazole (Sulfasuxidine) and phthalylsulfathiazole (Sulfathalidine), which are poorly absorbed and pass out in the feces. After absorption, the major metabolic alteration is acetylation of the primary amino group. Sulfonamides are excreted by the kidney, chiefly by means of glomerular filtration.

The principal toxic effects of the sulfonamides are allergic reactions and injury to the kidneys. Hypersensitivity may be manifested by fever, rash, granulopenia, thrombopenia, or hemolytic anemia. These may develop any time after the first week of therapy, or earlier in individuals who have received the drug previously. Cross-sensitivity to different sulfonamides is common. Damage to the kidney may result from two kinds of injury: (1) precipitation of the drug, especially its acetylated derivative, in the tubules, and (2)

development of hypersensitivity with the production of lower nephron nephrosis. Crystallization in the renal tubules is most likely to occur when an inadequate quantity of fluid is ingested or when the urine is acid, since the solubility of both acetylated and free forms is considerably greater in a neutral or alkaline medium. One method of avoiding renal injury is to maintain an adequate urine output—at least 1200 ml. per day. Another involves alkalinization of the urine by the oral administration of 12 to 15 Gm. of sodium bicarbonate per day. This procedure, however, increases the rate of excretion of sulfonamide, lowers the blood concentration, and may make it necessary to give larger quantities in order to produce the desired antibacterial effect. A third method of preventing precipitation in the urinary tract is to administer two or three sulfonamides concomitantly, since the solubility of each is independent of the presence of the others. This, however, may have a disadvantage, since *in vitro* the "triple sulfonamides" exhibit much less antibacterial activity than the single agents of which they are composed. Lower nephron nephrosis, a rare complication of sulfonamide therapy, usually occurs in patients who have taken one of these agents in the past. It may follow the ingestion of as little as 1 Gm. of drug and is a totally unpredictable and unavoidable accident for which there is no specific therapy. Of greatest importance in the management of this condition is careful adjustment of fluid intake; this should not exceed the quantity of urine plus the amount of insensible fluid loss in a 24-hour period. Attempts must not be made to "open up the kidney" by the parenteral administration of large quantities of water because of the danger of pulmonary edema and death. Another rare but serious manifestation of sulfonamide toxicity is acute hemolytic anemia. This may develop within 48 hours of therapy and is manifested by a rapid fall in the number of erythrocytes, rising icterus, high fever, and hemoglobi-

nuria. Drug administration should be discontinued at once and blood transfusions given.

Sulfadiazine (2-sulfanilamidopyrimidine) is absorbed from the gastrointestinal tract slowly and incompletely. Excretion by the kidney occurs more slowly than with some of the other sulfonamides. It is present in pleural, synovial, pericardial, peritoneal, and edema fluids. The tissue concentration is 60 to 75 per cent of that in the plasma. About 50 per cent of the drug is bound to protein, but there is no correlation between this and clinical effectiveness. Only small amounts of sulfadiazine are acetylated. It appears in the urine in both the free and acetylated forms. Neither is very soluble and crystalluria is common. For most types of systemic infection in adults, sulfadiazine is administered in a dose of 4 to 6 Gm. per day following an initial dose of 4 Gm. In young children 0.065 to 0.1 Gm. per pound of body weight per 24 hours usually produces an adequate effect; the initial dose should be about one-half of this quantity.

Sulfamerazine (4-methyl-2-sulfanilamidopyrimidine) is absorbed more rapidly and completely from the gastrointestinal tract than sulfadiazine. For these reasons the "loading" dose need be only 2 Gm. in most cases, and effective blood levels may be maintained by the administration of 1 Gm. every 6 to 8 hours. About 85 per cent of sulfamerazine is bound to plasma proteins The concentration in the tissues is 50 to 75 per cent of that in the plasma. Very little acetylation occurs, and the tendency to renal tubular damage and calculus formation is less than with sulfadiazine.

Succinylsulfathiazole (Sulfasuxidine) and *phthalylsulfathiazole* (Sulfathalidine) are poorly absorbable when given orally and are used primarily for the suppression of bacterial growth in the intestine. They are usually employed in the preparation of patients for bowel surgery or in the treatment of bacillary dysentery. In the latter, these agents are generally less effective than those which are well-absorbed like sulfadiazine, sulfamerazine, or sulfisoxazole (Gantrisin).

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phenicol), Terramycin (oxytetracycline), Achromycin (tetracycline), erythromycin, bacitracin, polymyxin, neomycin, novobiocin, and nystatin.

Testing of Organisms for Sensitivity to Various Antibiotics

The sensitivity of bacteria to various chemotherapeutic agents is determined by bacteriologic technics. The most accurate procedure for estimating the susceptibility of organisms to various drugs is the test-tube dilution method. For routine study, the filter paper disk method is the one most widely used in microbiology diagnostic laboratories, because it is easier to perform and yields results which, although only crude, are adequate for clinical purposes in most instances.

Determinations of the sensitivity of an organism to chemotherapeutic agents may be helpful in the management of an infectious disease. They are not necessary, however, in all or even in a majority of cases; furthermore, the results correlate only roughly with clinical response to chemotherapy. Nevertheless, this procedure is invaluable in some types of infection in indicating the choice of therapeutic agent and general level of dosage required. Specific indications for sensitivity testing of specific bacteria are discussed in the chapters of this book dealing with particular infections.

Resistance of Bacteria to Antibiotics

The acquisition of resistance of bacteria to various antibiotic agents is being observed with increasing frequency. One of the most important problems in this respect is *Staph. aureus*, many strains of which are rapidly becoming insensitive not only to penicillin but also to some of the so-called "broad spectrum" antibiotics. A recent study of 500 strains of *Staphylococcus aureus* isolated from patients in a large city hospital revealed that only about one-fourth were susceptible to penicillin; about two-thirds were sensitive to chlortetracycline (Aureomycin), a little more than half to oxytetracycline (Terramycin), and 70 per cent to streptomy-

Gantrisin (3,4-dimethyl-5-sulfanilamidoisoxazole) is more soluble than any of the compounds described above. It is absorbed rapidly from the gastrointestinal tract. About 30 to 35 per cent is acetylated; this derivative is much more soluble in water than the other sulfonamides in clinical use. The drug is distributed only in the extracellular water of the body and does not penetrate cells. Because of this, the administration of a given dose of this agent will yield a plasma concentration two times greater than an equal quantity of sulfadiazine or sulfamerazine. The daily dose and clinical effectiveness of Gantrisin are approximately the same as those of sulfadiazine. The incidence of renal crystallization and hematuria is smaller with Gantrisin than with the other commonly used sulfonamides; precautions must be taken, nevertheless, to insure an adequate fluid intake and urine output (at least 1200 ml. per day).

Elkosin (6-sulfanilamido-2,4-dimethylpyrimidine) is appreciably more soluble in urine over a wide pH range than either sulfamethazine or sulfadiazine. It has, in addition, a very low order of acetylation. For these reasons, it has been used in the treatment of urinary tract infections with favorable clinical and bacteriologic results.

Antibiotics

The development of antibiotics for the treatment of infections constitutes one of the most important advances in modern medicine. The course of many of the infectious diseases has been so altered by therapy with these agents that their textbook descriptions are relatively obsolete. Although a very large number of antimicrobial substances have been isolated from all types of microörganisms, plants, animal tissues, and other sources, many have proved too unstable or too toxic to have a clinical application. Among those which are clinically useful are penicillin, streptomycin, Aureomycin (chlortetracycline), *Chloromycetin* (chloram-

hydrazide occurs rapidly if this agent is used alone. A recent observation suggests, however, that such tubercle bacilli may have markedly diminished virulence for the guinea pig; whether these strains are also a virulent for man is not known. Combination of antibiotics may result in a diminution in the speed of emergence of resistance of bacteria to any of the drugs in a mixture. Organisms exposed *in vitro* to erythromycin alone rapidly become insensitive; if in contact with both erythromycin and penicillin, or erythromycin and streptomycin, these bacteria develop resistance to all of the agents at a much lower and slower rate. Clinical experience *indicates that the emergence of resistance in the tubercle* bacillus to streptomycin is considerably delayed by the simultaneous administration of para-aminosalicylic or isonicotinic acid hydrazide, or both.

Penicillin

Penicillin is an antibiotic produced by the mold *Penicillium* and is active primarily against gram-positive bacteria. It is available in pure crystalline form. The compound used most extensively is benzyl penicillin G and its procaine salt. One thousand units of the drug equals 0.6 mg. This antimicrobial substance is supplied in the form of the sodium salt, there being approximately 0.1 Gm. of sodium in 1,000,000 units, a factor to be kept in mind when dealing with patients whose salt intake needs to be restricted.

Penicillin may be administered by several routes: orally, intramuscularly, subcutaneously, intravenously, topically, or by inhalation. Application to the skin, especially of preparations dissolved in oily bases, is to be avoided wherever possible, because of the high risk of sensitization. The antibiotic agent may be given orally in the form of a buffered or unbuffered liquid or tablet. For intramuscular or intravenous use, penicillin is usually dissolved in physiologic saline solution. The procaine salt is probably the most extensively used preparation, because absorption is slowed

cin. The degree of resistance was least to chloramphenicol (Chloromycetin). In another study of this problem, it was found that untreated hospitalized individuals had a higher carrier rate of Staphylococcus aureus at the time of discharge than when they were admitted, and that they exhibited an increase in the percentage of organisms insusceptible to penicillin. The incidence of penicillin-resistant staphylococci in people outside the hospital is 10 to 15 per cent. It is important to stress the fact that strains of penicillin-insensitive *Staph. aureus* isolated from patients produce penicillinase and maintain their high state of resistance permanently.

Streptomycin treatment very commonly induces resistance in organisms. Some of the bacteria involved in urinary tract infections and *Hemophilus influenzae,* for example, may become totally insensitive to streptomycin within 3 or 4 days after the initiation of therapy. An increasing number of bacteria, both Gram-negative and Gram-positive, have been shown to develop varying degrees of lack of susceptibility to chlortetracycline (Aureomycin), chloramphenicol (Chloromycetin), oxytetracycline (Terramycin) and erythromycin.

Organisms which become insensitive to one antibiotic may simultaneously develop resistance to another. Thus, bacteria which lose their susceptibility to chlortetracycline (Aureomycin) not infrequently also exhibit insensitivity to oxytetracycline (Terramycin), chloramphenicol (Chloromycetin), and tetracycline (Achromycin). The development of neomycin resistance is quite readily associated with a significant loss of sensitivity of streptomycin. The reverse does not occur so regularly.

Streptomycin resistance has been studied most intensively in the tubercle bacillus. Tuberculous patients treated with this antibiotic alone usually develop totally resistant organisms in varying periods of time. The incidence of insensitive strains is about 75 per cent after three months of therapy. Development of insensitivity to isonicotinic acid

paramount importance in the exhibition of this agent by mouth is careful attention to the spacing of the doses in regard to meals. Penicillin G should not be given by mouth later than one-half hour before, or earlier than two and one-half hours after a meal. The subcutaneous or intramuscular injection of penicillin causes little or no local irritation, and the drug is absorbed very rapidly into the blood stream, from where it is either excreted by the kidneys or distributed evenly in the plasma and extracellular fluid. Normally, only minute amounts penetrate into the cerebrospinal fluid, but in the presence of meningeal inflammation, particularly when very large doses of penicillin are administered either intravenously or intramuscularly, appreciable levels of the drug may be obtained.

Penicillin is excreted by the kidneys with great rapidity, 90 per cent being cleared by tubular excretion. Carinamide retards penicillin excretion by blocking tubular function. When given orally in a dose of 2 to 3 gms. every 3 hours, it elevates blood levels of the antibiotic 2 to 5 fold. It may produce nausea and vomiting. Benemid is also very effective in prolonging the duration and increasing the concentration of penicillin in the blood. It is preferred over Carinamide because its use is accompanied by little or no gastric distress. The dose of Benemid is 0.5 gm. orally every 6 hours.

Penicillin is almost devoid of toxicity in human beings. It does produce, however, a number of untoward effects many of which are due to the development of hypersensitivity. These are described below.

The clinical uses of penicillin in specific infections are discussed in detail in other chapters of this book. The diseases in which this antibiotic is the drug of choice will, therefore, only be listed here. Acute and chronic gonorrhea, pneumococcal pneumonia, infections due to the beta-hemolytic *Streptococcus*, most cases of subacute bacterial endocarditis, fusospirochetal diseases, anaerobic streptococcal infections, anthrax, streptobacillosis, and all stages of

and detectable blood levels may be present for as long as 24 hours; with the addition of aluminum monostearate, the drug may be detectable in serum for 48 to 72 hours. In patients who have become sensitized to penicillin-G, the use of penicillin-O (allylmercaptomethyl penicillin) has been suggested. Some degree of cross reaction takes place between the two types of antibiotic, however, and one cannot be substituted for the other without caution. Solutions of crystalline penicillin G in physiologic saline may be inhaled for the treatment of various acute or chronic pulmonary infections. Two of the most recently developed types of penicillin are Bicillin (dibenzylethylenediamine dipenicillin) and Penicillin V. Bicillin may be administered orally or parenterally. When given by mouth, however, absorption is more erratic than that of penicillin G which yields 3 to 6 times the activity of Bicillin. The intramuscular injection of Bicillin, on the other hand, has the advantage of prolonging the duration of blood levels; the administration of 200,000 to 500,000 units may produce a detectable concentration of antibiotic in the blood for as long as 2 weeks. Penicillin V differs from G in a single oxygen molecule. Taken by mouth, penicillin V produces higher and more prolonged serum levels than the same quantity of penicillin G. Meals do not influence the absorption or destruction of the drug. Intramuscular injection of penicillin V yields lower blood concentrations than an equal amount of penicillin G. At the moment, penicillin V appears to be the drug of choice for oral administration, although its cost may influence its use.

Only about 20 per cent of an orally administered dose of penicillin G is absorbed into the blood stream, the remainder being destroyed by gastric acidity and by penicillinase in the lumen of the intestines. As a consequence, much larger doses are needed for oral than for parenteral therapy. Administration of alkalinizing agents with the drug apparently does not increase appreciably the amount absorbed. Of

little, if any, penetrates the blood-spinal fluid barrier when the meninges are normal. In the presence of meningeal inflammation, however, intramuscular injection produces detectable and sometimes effective levels of drug in the spinal fluid. After a single intramuscular injection, approximately 80 per cent of the antibiotic appears in the urine over a 24 hour period. Renal excretion is slower than that of penicillin.

The chief toxic reaction to the administration of streptomycin is damage to the eighth nerve. The larger the dose of drug and the more prolonged the treatment, the higher the incidence of this complication. The other untoward effects of streptomycin are discussed below.

The salts of streptomycin (hydrochloride, sulfate, or calcium chloride complex) are usually dispensed as dry sterile powders in airtight rubber-cap vials, each containing the equivalent of 1 or 2 Gm. of streptomycin base. There are three routes of administration: intramuscular, topical, and oral. Streptomycin is given by mouth when a local effect in the intestinal tract is desired, but this route is of no value in the treatment of systemic infections because so little is absorbed from the gastrointestinal tract. In the treatment of bacterial enteritis—bacillary dysentery for example—the antibiotic is usually administered orally in a dose of 0.25 gm. every six hours For systemic infections it is injected intramuscularly at 6 or 12 hour intervals. When treatment is required for only a few days, 3 or 4 gm. may be given per day; large doses should be avoided wherever possible, however, because of the increased danger of eighth nerve injury. In tuberculosis it is the present practice to give only 1 gm of streptomycin twice a week. Solutions for injection should contain no more than 0.5 gm. per ml., since higher concentrations often produce considerable pain. Intrathecal administration may be important in the management of meningitis due to organisms susceptible to this antibiotic agent The quantity instilled intraspinally should be dis-

syphilis are best treated with penicillin, although other chemotherapeutic agents *may* be effective. While many staphylococcal infections are now due to strains which are resistant to penicillin, this agent should probably still be the first used for treatment. Therapy with penicillin should continue until the sensitivity of the bacteria to various antibiotics has been determined; the drug showing the highest degree of effectiveness against the organism should then be given.

Streptomycin

Streptomycin is an antibiotic produced by *Streptomyces griseus*. It is active against both gram-positive and gram-negative organisms, the latter being more sensitive than the former. It is very active against the tubercle bacillus. Dihydrostreptomycin is a derivative of streptomycin produced by catalytic hydrogenation. It has been used in place of streptomycin because it was believed to be less neurotoxic. However, damage to the auditory nerve following dihydrostreptomycin therapy is as frequent as that following streptomycin when full doses are employed. Streptomycin affects the vestibular portion, while dihydrostreptomycin produces damage to the cochlear portion of the eighth nerve. Dihydrostreptomycin is as effective as streptomycin in the treatment of tuberculosis and all other susceptible infections. The dihydro- derivative appears to cause fewer hypersensitivity reactions than the parent drug and can be administered to patients who are sensitive to the latter.

Streptomycin is a basic substance and is usually prepared in the form of a hydrochloride or sulfate which is readily soluble in water. The drug is poorly absorbed from the gastrointestinal tract; after oral administration, most of it is passed out in the feces, only traces being demonstrable in the blood and urine. Parenteral injection leads to an even distribution of the agent in extracellular body fluids, but very

little, if any, penetrates the blood-spinal fluid barrier when the meninges are normal. In the presence of meningeal inflammation, however, intramuscular injection produces detectable and sometimes effective levels of drug in the spinal fluid. After a single intramuscular injection, approximately 80 per cent of the antibiotic appears in the urine over a 24 hour period. Renal excretion is slower than that of penicillin.

The chief toxic reaction to the administration of streptomycin is damage to the eighth nerve. The larger the dose of drug and the more prolonged the treatment, the higher the incidence of this complication. The other untoward effects of streptomycin are discussed below.

The salts of streptomycin (hydrochloride, sulfate, or calcium chloride complex) are usually dispensed as dry sterile powders in airtight rubber-cap vials, each containing the equivalent of 1 or 2 Gm. of streptomycin base. There are three routes of administration: intramuscular, topical, and oral. Streptomycin is given by mouth when a local effect in the intestinal tract is desired, but this route is of no value in the treatment of systemic infections because so little is absorbed from the gastrointestinal tract. In the treatment of bacterial enteritis—bacillary dysentery for example—the antibiotic is usually administered orally in a dose of 0.25 gm. every six hours. For systemic infections it is injected intramuscularly at 6 or 12 hour intervals. When treatment is required for only a few days, 3 or 4 gm. may be given per day; large doses should be avoided wherever possible, however, because of the increased danger of eighth nerve injury. In tuberculosis it is the present practice to give only 1 gm of streptomycin twice a week. Solutions for injection should contain no more than 0.5 gm. per ml., since higher concentrations often produce considerable pain. Intrathecal administration may be important in the management of meningitis due to organisms susceptible to this antibiotic agent The quantity instilled intraspinally should be dis-

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solved in 10 ml. of physiologic saline solution; this is administered every 12 to 24 hours for two or three days, depending on the clinical situation.

In localized areas of suppuration, such as empyema, it is probably best to inject the antibiotic into the local area of infection, as for example, into the intrapleural space.

Specific indications for the use of streptomycin in various diseases are described in other chapters of this book. Streptomycin is highly effective in the therapy of infections due to *Pseudomonas*, *Klebsiella*, *Pasteurella* (tularemia and plague), and in tuberculosis. It may be of help in an occasional case of urinary tract infection. In some clinics it is the agent of choice in the therapy of meningitis due to *H. influenzae* and is given by both the intramuscular and intrathecal routes.

Chlortetracycline (Aureomycin)

This antibiotic is a product of *Streptomyces aureofaciens*. It is a remarkable antibacterial agent because of its wide range of activity, encompassing not only many gram-positive and gram-negative bacteria but also the *Rickettsiae* and some of the larger viruses. Many strains of *Staph. aureus* and some of the gram-negative bacteria like *Proteus* and *Pseudomonas* may become rapidly insensitive to the drug. Aureomycin is a basic substance but is usually prepared in the form of a hydrochloride, which is strongly acid in reaction. The dry salt is stable, but in solution it deteriorates rapidly, especially if the pH is above 6. Absorption from the gastrointestinal tract is rapid but inefficient, as a result of destruction of the antibiotic by intestinal contents. After a single oral dose, Chlortetracycline can be demonstrated in the urine within 15 minutes and for as long as 24 hours. Concentrations in the plasma fall rapidly below detectable levels. The drug diffuses into the spinal fluid but in smaller amounts than into the plasma. Subcutaneous injection is not feasible because of the severe irritation which is produced.

Intravenous administration of buffered solutions is possible, but there is some risk of phlebitis. When taken by mouth, this agent produces nausea and vomiting occasionally. Aluminum hydroxide should not be given to control gastric irritation, because it reduces the serum level of the antibiotic by 80 per cent or more. The ingestion of milk or food produces the desired effect without altering the quantity of drug in the plasma. Mild diarrhea associated with loose, bulky stools may result from local irritation or alteration in the bacterial flora of the intestinal tract. Some of the untoward effects which follow the exhibition of Aureomycin are discussed below.

The dose range of the Aureomycin is from 1 to 6 gms. per day, given in divided quantities at 6 or 8 hour intervals; in most clinical infections amounts larger than 1 gm. per day are probably not necessary. The dose for intravenous administration is about one-third to one-fifth as large as the oral one.

The most impressive clinical results with Aureomycin have been observed in rickettsial disease, brucellosis, lymphogranuloma venereum, acute peritonitis, bacterial pneumonias, and some penicillin-resistant staphylococcus infections. Urinary tract infections in which the bacteria are penicillin- and streptomycin-resistant may be beneficially affected. This antibiotic has been used in the treatment of amebiasis; for maximal effect, it is probably best combined with another amebicidal drug.

Oxytetracycline (Terramycin)

Terramycin is very closely related chemically to chlortetracycline (Aureomycin). It may be administered orally or intravenously and is relatively stable over a wide range of temperature and hydrogen ion concentration.

The most commonly used form of Terramycin is the capsule of the crystalline hydrochloride salt. Parenteral and topical preparations are also available. Intravenous injection

of this antibiotic should be reserved for instances of severe illness or for cases in which it cannot be taken by mouth; unbuffered solutions should never be administered, because of the high degree of acidity.

Terramycin is absorbed rapidly from the gastrointestinal tract; antibacterial activity appears in the serum within one hour of oral administration. Meals do not influence the plasma concentration. A single oral dose may produce detectable concentrations in the blood for as long as 24 hours. Cumulative effects do not appear even after repeated daily doses of 1 gm. every 6 hours. When 250 mg. of the drug are given at 6 hour intervals, blood levels range between 5 to 10 μg. per ml. throughout the 24 hour period. Intravenous injection produces serum levels of from 5 to 10 μg. per ml. at the end of one hour and from 1 to 5 μg. per ml. after 12 hours.

The clinical applications of Terramycin are practically the same as those for Aureomycin (chlortetracycline). There is very little difference in the antibacterial activity of these two agents. Some clinical experience indicates that oxytetracycline disturbs the normal bacterial population of the intestinal tract with the development of severe enteritis frequently due to *Staphylococcus aureus* more frequently than any other antibiotics. The other complications of treatment with Terramycin are described below.

Tetracycline (Achromycin)

Achromycin is closely related chemically to both Aureomycin (chlortetracycline), and Terramycin (oxytetracycline) and has about the same range of antimicrobial activity. It is essentially the skeleton structure of these two antibiotics and is prepared synthetically. Achromycin is useful in the infections which respond favorably to either Aureomycin or Terramycin. The incidence of side reactions, such as nausea, vomiting, and diarrhea, is said to be lower with tetracycline than with its related drugs. The develop-

ment of bacterial resistance to Achromycin is accompanied by simultaneous loss of sensitivity to other agents.

Achromycin is stable in solution. It is available in the form of the crystalline hydrochloride in capsules, dispersible powder, and for parenteral use. Intravenous therapy should be employed only in patients unable to take medication by mouth. The average adult dose is 500 mg. intravenously at 12 hour intervals; this may be increased to a maximum of 500 mg. every 6 hours depending on the severity of the disease. For oral treatment, 1 to 2 gms. divided into 4 doses per day is usually adequate. Achromycin is said to penetrate the blood-brain barrier with relative ease, and spinal fluid levels approximately 4 times higher than those obtainable with equal quantities of Aureomycin have been reported.

Chloramphenicol (Chloromycetin)

The initial preparations of Chloromycetin were obtained from cultures of *Streptomyces venezuelae*. The drug has been isolated in pure crystalline form and synthesized. There is no difference in the antibacterial activity of the synthetic and the natural products. Chloramphenicol is a white, neutral crystalline powder which is stable in the dry state. It is soluble to a concentration of approximately 0.25 per cent in water and up to 15 per cent in propylene glycol.

Chloramphenicol is usually administered orally, although preparations are available for intramuscular or intravenous injection. The fact that this agent may occasionally depress the bone marrow does not contraindicate its use but suggests that it be employed only when indicated. The drug is rapidly absorbed from the gastrointestinal tract, appearing in the blood within a few minutes. The maximal concentration occurs at the end of 2 hours but some may still be found after 16 or 24 hours About 80 per cent of an oral dose can be demonstrated in the urine, although only about 15 per cent is still biologically active.

A large number of organisms are susceptible to chloram-

phenicol. Although it is active against some types of gram-positive bacteria, staphylococci which are resistant to other antibiotics for example, it is most effective against the *Rickettsiae* and gram-negative organisms. *Staph. aureus* and coliform and other enteric organisms may become resistant to this antibiotic.

Chloramphenicol has been employed most extensively in the therapy of brucellosis and rickettsial diseases. It probably has its greatest field of usefulness in typhoid fever, where it is the most effective available drug, and for the management of antibiotic-resistant staphylococcal infection. It has also been used for the treatment of urinary tract infections due to *E. coli*, *A. aerogenes*, and other gram-negative organisms, particularly those which have become insensitive to streptomycin and other drugs.

Aside from the mild gastrointestinal irritation which is produced by chloramphenicol, the most serious untoward effect is depression of the bone marrow. Granulopenia develops first and is followed by aplastic anemia, if administration of the drug is continued; this is rare. The other complications of chloramphenicol therapy are discussed below.

Erythromycin (Ilotycin)

Erythromycin is an antibiotic elaborated by *Streptomyces erythreus*. It is soluble only to the extent of 2 mg. per ml. in water but is highly soluble in alcohols and in a number of other organic solvents. The drug retains its activity in solution at 4°C. for at least 8 weeks; at room temperature, there is some deterioration during the first week but not for the next two months. Erythromycin is not affected by substances which are known to inhibit penicillin, streptomycin, and the sulfonamides.

Erythromycin is well absorbed from the intestinal tract; the drug is usually given, therefore, by mouth. Peak serum

concentrations appear in 1 or 2 hours after ingestion of a dose and decline rapidly so that the agent is no longer demonstrable after 4 to 6 hours. Only small amounts are recovered from the urine.

Gram-positive organisms, including *Staph. aureus*, are highly sensitive to erythromycin, being inhibited, on the average, by concentrations of less than one µg. per ml. Strains of gram-negative bacteria such as *Neisseria*, *Hemophilus*, and *Brucella* are inhibited by 6 µg. or less per ml. The antibiotic also appears to be active against various *Rickettsiae*, *E. histolytica*, and the virus of lymphogranuloma venereum. In general, pneumococci and group A hemolytic streptococci are the most sensitive. Coliform organisms, *Proteus*, and *Pyocyaneus* are quite resistant.

In clinical practice, the use of erythromycin should be restricted to the treatment of infections due to gram-positive organisms. Since penicillin is so highly effective in disease due to pneumococci and beta-hemolytic streptococci and no penicillin-resistant strains of these bacteria have yet been discovered, erythromycin need not be given in these infections, except when patients are known to have had reactions to penicillin. Strains of *Staphylococcus aureus* which are insensitive to all other antibiotics may be highly susceptible to erythromycin. This agent is, therefore, most valuable in the management of disease produced by staphylococci or other penicillin-resistant gram-positive organisms.

Bacteria exposed to erythromycin may become insensitive quite rapidly. *In vitro* studies have suggested that the emergence of resistance to erythromycin is considerably delayed and diminished if organisms are exposed to mixtures of this antibiotic with other antimicrobial drugs. Because of this, it is probably best, in clinical practice, especially when treating staphylococcal infections, not to administer erythromycin alone but to give chloramphenicol or other agents simultaneously.

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to 0.5 gm. It is not absorbed from the bowel, from which it eliminates sensitive organisms. Polymyxin does not pass into the cerebrospinal fluid and cannot be detected in the bile or in the urine in biologically active form. It is toxic to the kidney; renal damage becomes evident on about the fourth or fifth day of treatment in a significant number of patients. Only proteinuria or oliguria may be present, or nitrogen retention may appear. Some preparations of the antibiotic are relatively free of the renal-damaging effect. Because of the danger of nephrotoxicity, polymyxin should be employed only when other antimicrobial agents are ineffective and when the patient's life is in jeopardy. Impressive clinical results have been produced in some cases of *Pseudomonas* aeruginosa bacteremia and meningitis.

Neomycin

Neomycin, an antibiotic derived from a strain of streptomycetes closely related to *Streptomyces fradiae*, is bactericidal *in vitro* against a wide variety of both gram-negative and gram-positive organisms. The drug may be administered by both the oral and parenteral routes Absorption from the intestinal tract is relatively poor The usual oral dose is 2 gms per day, the intramuscular one is 1 to 2 gms. in 24 hours.

The clinical usefulness of neomycin is limited by its potential toxicity. Kidney and eighth-nerve damage occur in a not insignificant number of patients. In view of these untoward effects, neomycin should *never* be the first drug employed in the treatment of any infection. It should be reserved for use in those diseases in which no other antibiotic is effective and the situation threatens life. The magnitude of the risk of renal or auditory-nerve injury must always be weighed against that of the untreated infection. If used critically and intelligently, neomycin may be lifesaving.

Bacitracin

Bacitracin is a polypeptide antibiotic produced by a strain of *Bacillus subtilis*. The bacterial spectrum resembles that of penicillin. The drug is soluble in water or physiologic saline solution. It is most frequently applied topically in various types of ointment. For systemic administration it is usually dissolved in 2 per cent Novocaine in physiologic saline solution.

Very little bacitracin is absorbed from the gastrointestinal tract, although it inhibits the growth of many bacteria in the bowel, including *Clostridia* and gram-positive cocci. The antibiotic appears in the blood and tissues, but very little diffuses into the cerebrospinal fluid after intramuscular injection. It is excreted slowly and unlike penicillin, plasma concentrations may remain elevated for several hours.

Bacitracin has its greatest clinical application in the topical therapy of infections due to *Staph. aureus* and other gram-positive bacteria, particularly those resistant to other antibiotics. Systemic disease caused by strains of staphylococci insensitive to other chemotherapeutic agents is an indication for the parenteral administration of the drug. The intramuscular dose is 15,000 to 20,000 units given 4 times a day Larger quantities increase the risk of serious renal damage. Careful attention must be paid to the development of nephrotoxic manifestations; if kidney dysfunction becomes appreciable, treatment should be discontinued.

Polymyxin (Aerosporin)

Polymyxin is a polypeptide antibiotic obtained from *Bacillus polymyxa* The principal effect is upon gram-negative bacilli, for which it is one of the most potent chemotherapeutic agents available; strains of *Proteus* are, however, resistant. The drug is usually administered intramuscularly at intervals of 8 or 12 hours, the total daily dose being 0.2

Trichophyton are inhibited by concentrations of 0.5 to 2 units per ml. Bacteria are not affected by the drug.

Nystatin is poorly absorbed from the gastrointestinal tract but high blood levels follow intravenous injection. It is employed for local application in the form of ointments, solutions, powders, suppositories, and gels. Treatment of *Candida* of the skin and vagina has been reported to be successful after topical use. The drug has been given orally to reduce the number of fungi in the intestine which may increase after the administration of antibacterial agents, particularly the tetracyclines. There is considerable doubt, however, that increase in yeasts in the bowel is related to the production of intestinal disorders. Tetracycline compounds have been combined with nystatin (Mysteclin) in an attempt to prevent the overgrowth of yeasts and fungi in the intestinal tract. Such therapy produces the desired mycological effect, but there is no evidence that it needs to be employed in the average patient receiving a tetracycline compound. It may have a place, however, in the treatment of infections in patients with diabetes mellitus, debilitated individuals, and premature infants because of the increased susceptibility to mycotic disease which such individuals exhibit.

The usual oral dose of nystatin is 150 mg. (500,000 units) 3 times a day. Although an occasional case of disseminated mycotic infection has been treated parenterally with reported good results, the place of this agent in the therapy of deep-seated mycoses still remains to be determined.

There is little or no evidence of toxic reactions following the oral or local administration of nystatin. Nausea, vomiting, and diarrhea have been noted occasionally.

Nitrofurantoin (Furadantin)

Furadantin is an antibacterial agent of value primarily in the treatment of some types of urinary tract infection. It is

Novobiocin (Cathomycin, Streptonivicin, Albamycin, Cardelmycin)

This antibiotic is a dibasic substance, the exact chemical composition of which is not known; its salts are water soluble. *In vitro*, it inhibits the growth of many strains of *Staph. aureus* resistant to other antimicrobial agents, *Strep. pyogenes*, *Brucella*, the pneumococcus, the meningococcus, *H. pertussis*, *Pasteurella*, and *Proteus*. There is a marked decrease in antibacterial activity in the presence of serum. Absorption from the intestinal tract is rapid. Excretion is slow, appreciable amounts of drug being detectable in the serum 24 hours after a single dose.

Most investigators have recommended that the use of novobiocin be restricted to the treatment of staphylococcal infections due to strains which are resistant to other antibiotics, because it has no advantages over other drugs when employed for the eradication of other sensitive organisms. However, *Proteus* is significantly susceptible to novobiocin, and its use in infections due to strains of this organism not sensitive to other agents is indicated. Staphylococci become resistant to novobiocin rapidly. For this reason, it is best not to administer this drug alone but to give it together with another antibiotic to which the infecting strain is sensitive. The usual dose of novobiocin is 0.5 gm. at 6 hourly intervals orally, or 1 to 2 gms., in equally divided doses, intramuscularly. Severe eruptions and high fever are not uncommon untoward effects of the drug.

Nystatin (Mycostatin)

Nystatin (Mycostatin) is elaborated by *Streptomyces noursei*. It is a pale yellow substance, soluble to the extent of 10 to 20 units per ml. of water. Strains of *Candida, Blastomyces, Histoplasma, Microsporum, Epidermophyton,* and

Trichophyton are inhibited by concentrations of 0.5 to 2 units per ml. Bacteria are not affected by the drug.

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Nitrofurantoin (Furadantin)

Furadantin is an antibacterial agent of value primarily in the treatment of some types of urinary tract infection. It is

poorly soluble in water, although the higher the pH, the larger the quantity that will dissolve. The drug is bacteriostatic; in high concentrations, or in low ones in special instances, it is bactericidal. It is most active against *E. coli* (bactericidal), of intermediate effectiveness against *A. aerogenes*, and completely without effect against *Ps. aeruginosa* (*Ps. pyocyanea*). Activity against *Proteus* is variable, although many strains are quite sensitive. *Staph. aureus* and enterococci are inhibited by low concentrations.

Furadantin is administered orally, usually in a dose of 7 to 10 mg. per Kg (100 to 200 mg. 4 times a day). Useful blood levels cannot be produced. The drug is excreted in the urine. Within 4 to 6 hours after a maximal clinical dose, the concentration in the urine is 25-50 mg. per 100 ml.; 8 hours after a dose, the levels are low. In highly alkaline urine, as is the case in *Proteus* infection, the inhibitory effect of furadantin appears to be depressed; for this reason, the simultaneous administration of an acidifying agent has been suggested The development of bacterial resistance has not been noted.

The infections of the urinary tract which respond most favorably to therapy with furadantin are those which are acute and uncomplicated. In chronic cases, especially those with complicating conditions in the urinary tract, the response is not so good. Infections produced by *E. coli* are the most easily eradicated. Those due to *Ps. aeruginosa* are totally unaffected, and those in which *A. aerogenes* is involved occupy an intermediate position. *Ps aeruginosa* may appear in the urine for the first time during treatment with furadantin. Although the drug has been said to be most active against *Proteus* infection, the results are quite variable. Not infrequently, this organism is only temporarily suppressed and reappears after cessation of therapy. Furadantin is relatively non-toxic. Nausea, with or without vomiting, is the commonest untoward reaction. Various types of skin eruptions have been described.

Tuberculostatic Drugs

Para-aminosalicylic Acid (PAS): Para-aminosalicylic acid, a white crystalline powder, is sparingly soluble in water but easily dissolved in the form of its sodium salt. It has a marked bacteriostatic effect *in vitro* against many strains of *M. tuberculosis*, even those which have become streptomycin-resistant. The anti-bacterial activity is partially decreased by para-aminobenzoic acid.

Para-aminosalicylic acid and its sodium salt, when given orally, are rapidly absorbed and quickly excreted. It is necessary to give the drug frequently in order to reach and maintain adequate blood levels. A single dose produces maximal serum concentration within 30 to 60 minutes of administration, but the drug is not present in the blood after 2 to 3 hours. PAS attains high concentrations in the interstitial tissues of the pulmonary alveoli, in the liver, and in the kidney, and also diffuses into the cerebrospinal fluid and the pleural cavity. The quantities are smaller in tuberculous cavitation than in normal lung. Para-aminosalicylic acid is almost entirely excreted by the kidney either unchanged or in the acetylated form.

Para-aminosalicylic acid is usually given orally. Since considerable gastric irritation may result from the large quantities necessary, the concurrent administration of various types of alkali or milk is advisable. Various mixtures containing flavoring and alkalizing compounds have been employed. Preparations for intravenous use are also available; these should be reserved for patients in whom severe gastric distress prohibits oral use or for those in whom coma is present. The usual oral dose is 8 to 12 gm. per day in divided doses. PAS is used together with either isonicotinic acid hydrazide (INH) or streptomycin, or both, in the therapy of tuberculosis. Tubercle bacilli may become resistant to para-aminosalicylic acid if this drug is used alone. Combination with streptomycin or INH delays remarkably

the speed of emergence of resistance of the organisms to all of the tuberculostatic agents and produces an additive antimicrobial effect. The excretion of PAS is blocked by Carinamide and Benemid. The use of these agents is helpful when high blood levels cannot be obtained because of inability of a patient to ingest large enough quantities.

The most common toxic effects of para-aminosalicylic acid are nausea, vomiting, and burning epigastric distress. Diarrhea occurs occasionally. Toxic damage to the liver and potassium deficiency have been recorded. Hypoprothrombinemia has been noted when large quantities (30 gm. per day) have been given; the administration of synthetic vitamin K is preventive and curative. Tinnitus and reduction in the acuity of hearing may develop occasionally but disappear rapidly after cessation of treatment.

Isonicotinic Acid Hydrazide (INH): Of all the tuberculostatic agents, isonicotinic acid hydrazide has the highest activity *in vitro*. It is not effective against organisms other than *Mycobacteria*. The drug is administered orally, as a rule, and is almost completely absorbed from the digestive tract. Peak serum concentration occurs from 1 to 3 hours after administration. The drug is well distributed in the various body fluids and is not inactivated by them; it is present in sputum, urine, pleural exudate, plasma, and cerebrospinal fluid in active form. In cases of meningeal inflammation, the quantities of INH in the spinal fluid may be larger than those in the plasma.

Tubercle bacilli acquire resistance to isonicotinic acid hydrazide readily. Insensitive strains are recovered from some tuberculous patients who receive this drug alone for 1 to 2 months. There is no cross-resistance between INH, streptomycin, and PAS.

When INH is given alone in pulmonary tuberculosis, remarkable improvement for 1 to 2 months is followed in some cases by a static condition or clinical regression. This is often related to the emergence of drug-resistant tubercle

bacilli. For this reason, this agent should be given in combination with streptomycin or PAS.

A number of untoward effects have been noted following administration of INH. These include drowsiness, hyperreflexia, tremor of the limbs, twitching of the legs, difficulty in initiation of micturition, nausea, abdominal discomfort, transient flushing of the face, pruritic skin eruptions, peripheral neuropathy, acute pellagra, toxic hepatitis with jaundice, temporary arterial vasospasm, and mild psychotic reactions.

Selection of a Chemotherapeutic Agent

The physician is required to choose the treatment for an infectious process from an ever-increasing number of antibacterial drugs. In order to obtain the best results, it is essential that he have a working knowledge of the common pathogenic microorganisms. While cultural studies are desirable in every case, they are not always practicable. In many instances the etiology can be inferred from the onset and the clinical features of the disease Nevertheless, it must be stressed that careful bacteriologic studies are essential to proper treatment, and the conscientious physician must take whatever steps are required to obtain experienced bacteriologic help.

Even when the etiology of an infectious process is determined, selection of an appropriate drug does not follow automatically, because there may be wide variations in susceptibility among organisms of the same or related species. For example, it is not uncommon for different strains of a single species of bacteria to exhibit varying degrees of sensitivity to various antibiotics. Cost of a drug is also an important consideration. The nature of the illness may also affect the choice of agent; for example, an orally administered drug may be unsatisfactory in a patient who is vomiting. In critically ill individuals, it is sometimes necessary to

give a combination of drugs until cultural and sensitivity studies reveal which one is specifically indicated. In such cases, cultures should always be taken BEFORE INITIATION OF THERAPY. If a person has previously shown hypersensitivity or any other serious reaction to a drug or develops such untoward effects during treatment, a different agent should be used, if possible. The agents used in the management of specific infections are discussed in the chapters of this book dealing with these diseases.

THE COMPLICATIONS OF ANTIBIOTIC THERAPY

The complications of antibiotic therapy may be classified into three groups on the basis of the mechanisms involved in their production. First, there are those which are due to sensitization; these vary in severity from mild skin rashes which do not influence the course of the primary disease to situations which are so severe that they threaten life. The second group is related to toxic and irritating effects of the drugs and includes irritation of the gastrointestinal tract, local reactions at sites of injection, toxic depression of bone marrow and direct injury to nerves. The third category encompasses those reactions which have their basis in chemotherapeutically-induced biological alterations in either the infecting agent or in the host and lead to the development of metabolic defects, superinfection, drug-resistance, and depression of immune reponses

Reactions Due to Hypersensitization

Reactions due to hypersensitization are among the most common of the untoward sequelae that follow the use of practically all of the antibiotic agents. They occur in 2.5 to 5 per cent of patients who receive penicillin, being commonest after the intramuscular injection of the procaine salt and least frequent when penicillin is given by mouth. These reactions usually occur after 10 to 12 days of treat-

ment. They may appear in the absence of previous exposure to a drug or promptly after administration of the first dose; this is particularly true of penicillin. Although elimination of the drug usually results in rapid disappearance of the allergic manifestations, they may persist for 1 to 2 weeks or longer after therapy has been stopped. In some instances, the reaction is mild and disappears even while administration of the chemotherapeutic agent is continued. In others, it is of serious import and necessitates immediate cessation of treatment. In a few cases, it is necessary to interdict the use of the offending agent at some later time, because of the risk of death.

Untoward reactions to antimicrobial agents occur most commonly in the skin and are due, for the most part, to sensitization; they are often accompanied by fever and pruritus. Morbilliform rashes are the most frequent, but scarlatiniform, urticarial, vesicular or bullous eruptions may also be observed. These are of relatively minor importance unless they progress to more serious lesions. Their development may not necessitate cessation of therapy or contraindicate the use of the provoking drug later in the patient's life. Contact dermatitis may follow exposure to many of the antibiotic agents, it has been observed frequently in pharmacists, physicians and nurses who handle streptomycin or penicillin, even though they may have never received either of these agents orally or parenterally. In addition to edema, vesicle formation or eczema of the hands and face, rhinitis, and asthmatic breathing may be present. Contact dermatitis frequently results from the ill-advised application to the skin of antibiotics in suspension or solution in fat or oil vehicles The incidence of local and systemic allergic reactions following such treatment is higher than that which occurs when the agents are given by any other route, and this type of therapy should be avoided, wherever possible. Among the more serious skin reactions to antimicrobial drugs are purpura, exudative erythema multiforme, and exfoliative der-

matitis. These have been observed most often after the use of penicillin, streptomycin, and chloramphenicol. Although purpuric lesions may be secondary to thrombocytopenia, they are present most often without an accompanying platelet deficiency. This does not, however, decrease the importance of this lesion, because its development may indicate a serious degree of vascular injury. In some cases, the purpuric eruption is a component of generalized serum sickness. *Erythema multiforme exsudativum* has been observed most commonly with the sulfonamides; it occurs rarely, however, with the other antibacterial agents and may be extensive, of the vesiculo-bullous type, and produce severe constitutional reactions. The most serious skin lesion which results from the administration of antibiotics is exfoliative dermatitis. This is very often of severe degree, extremely incapacitating and may be fatal, unless promptly and properly treated; its appearance necessitates immediate cessation of chemotherapy.

In the management of allergic skin reactions, the most important single procedure is discontinuation of chemotherapy whenever possible. With the present availability of a number of antimicrobial agents, several of which may be effective against a specific organism, a change in therapy can frequently be made without seriously compromising the outcome of an infectious disease. The antihistaminic drugs may be helpful, particularly in combatting pruritus; occasionally they reduce the severity of the lesions or limit their spread. ACTH and cortisone may be beneficial, and are sometimes lifesaving in exfoliative dermatitis or in extensive and severe urticarial or bullous eruptions. These hormones also relieve the pruritus and edema, but they have not proved very helpful either in the prevention or limitation of most of the other lesions of the skin. The advisability of ACTH or cortisone therapy must be evaluated in relation to the state of activity of the infectious process

because of the tendency of these agents to favor the persistence or spread of infection.

"Drug fever" may be the only manifestation of sensitization to an antibiotic or may precede or accompany other reactions. The rate of disappearance of the fever after treatment has been stopped is directly related to the speed with which the causative drug is excreted. Fever tends to recur if the agent which first provoked it is again given.

Although many of the disturbances which occur in the mouth are due to irritative and toxic effects of the antibacterial agents, some are the result of sensitization. Oral complications of chemotherapy are observed most often following the use of the so-called "broad-spectrum" antibiotics—Aureomycin (chlortetracycline), Terramycin (oxytetracycline), and chloramphenicol. A common lesion is ulcerative or vesicular stomatitis. This is characterized by dryness, burning, soreness, itching, redness, and vesicle formation in the buccal mucous membrane, the tongue is red, smooth, shiny, and swollen. Angular stomatitis has been ascribed to drug-induced riboflavin deficiency but it is probably due to an allergic reaction, since the administration of large doses of this vitamin fail to cure it. Black or brown furring of the tongue follows changes in the oral microbial flora with increase in yeast-like organisms. Such fungi are not always present, however, and it has been suggested that the discoloration may be due to sensitization. Although lesions of the mouth may occur after the systemic administration of antibiotics, they are observed most frequently when local therapy, lozenges or troches, is used.

The most serious allergic complications which follow the exhibition of antibiotic agents, especially penicillin and streptomycin, are the Arthus reaction, angioneurotic edema, serum sickness, and anaphylaxis. Local edema, inflammation, and occasionally necrosis, which increases in intensity with successive injections unless therapy is stopped, re-

semble the Arthus phenomenon. In the most severe cases, extensive sloughing of skin and muscle may occur. Angioneurotic edema of the lips, tongue, face, and periorbital tissues, not infrequently accompanied by asthmatic breathing, has been noted after injection, inhalation, or other exposure to antimicrobial agents. Typical "serum sickness" has been observed following sensitization to penicillin and less often after streptomycin administration. The repository types of penicillin, especially those suspended in oil, are most often involved. The clinical picture varies in severity from mild fever, rash, and leukopenia to one in which severe arthralgia, purpura, lymphadenopathy, splenomegaly, electrocardiographic changes, edema, albuminuria, and hematuria in various combinations may be present. The reaction usually appears after chemotherapy has been given for one week or longer, the first manifestations may be delayed, however, until a week or two after treatment has been stopped.

Reports of acute anaphylactoid reactions to antibiotics, some of them fatal, have been appearing with increasing frequency. It has recently been estimated that there have been at least 1000 deaths in the United States as a result of anaphylaxis resulting from the administration of antimicrobial agents The drug which is most often implicated is procaine penicillin, but crystalline benzyl penicillin G, Bicillin, and streptomycin may also be responsible. Oral preparations of penicillin are least likely to cause anaphylactoid reactions. A rare reaction of this type has been described with Aureomycin. This phenomenon has not been observed following the use of tetracycline, chloramphenicol, bacitracin, polymyxin, neomycin, or furadantin. Individuals most prone to develop anaphylaxis are those with a history of asthma, hay fever or other allergies. Patients who have experienced anaphylactoid episodes should never again be exposed to the offending agent, unless this is absolutely unavoidable. Even a skin test with the drug or attempts at

desensitization may be very dangerous and should not be carried out unless the physician is ready to treat anaphylactic shock.

Eosinophilia has been ascribed to sensitization to antibiotics. It may be present as an isolated finding or be associated with other allergic manifestations. Although the sulfonamides were the first antimicrobial agents to be incriminated in the pathogenesis of polyarteritis nodosa and disseminated lupus erythematosus, sensitization to penicillin, streptomycin, and other antibiotics has recently been suggested as a possible etiologic background of these diseases.

For the most part, hypersensitivity to an antibacterial drug is highly specific for the particular agent, but, in certain cases, it may be elicited by closely related substances. Penicillin O produces a reaction in more than a third of the patients sensitive to penicillin G, and vice versa. Terramycin elicits a cross fixed reaction in individuals previously sensitized to Aureomycin. On the other hand, dihydrostreptomycin may be given to most but not all persons who have previously developed hypersensitivity to streptomycin, and vice versa

The prognosis in cases of sensitization to antimicrobial agents is variable and often unpredictable. Many patients, especially those who have had fever and rashes following the use of penicillin and who have been considered sensitive to the drug, have subsequently tolerated treatment with this agent without untoward effects. This may be due to differences in the form of the drug employed in the first and in the later treatment, and has been particularly true when sensitization has been the result of a repository type of preparation such as procaine penicillin (with or without aluminum monostearate) and when purified salt of crystalline penicillin G was used later Patch, endermal, and conjunctival tests for sensitivity yield variable results which cannot always be correlated with the effects observed on subsequent administration of the agent. Attempts to desensi-

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use may be accompanied by albuminuria, cylindruria, hematuria, and reduction in renal function which may be progressive, particularly in those with prior kidney damage. These changes are usually reversible if they are detected early and treatment is stopped; continuation of therapy in the face of increasing renal dysfunction may result in death.

Toxic or irritative effects of antibiotic agents occur in any part of the gastrointestinal tract. Severe stomatitis and glossitis may be due to irritation produced by antimicrobial drugs applied locally in the form of lozenges or troches. Disturbances in the function of the digestive tract are seen most often after the use of Aureomycin (chlortetracycline), Terramycin (oxytetracycline) and chloramphenicol. The ingestion of these agents may provoke a varying degree of nausea, vomiting and diarrhea which is probably due to direct irritation of the stomach and intestine, reduction in dose or administration of the antibiotic with milk or food frequently decreases the incidence and severity of the gastrointestinal symptoms. Penicillin and streptomycin given orally in comparable doses may induce heartburn, nausea, vomiting, and diarrhea. Tetracycline (Achromycin, Tetracyn) produces digestive difficulties less commonly than the other "broad-spectrum" drugs; these are also infrequent with erythromycin. Severe diarrhea with sanguino-purulent stools and marked constitutional reaction or shock following the use of antibiotics are usually due to acute enteritis, often staphylococcal, which results from superinfection.

The liver is occasionally affected by antimicrobial agents. Although hepatitis has followed the administration of streptomycin, it has not been determined definitely whether this was not "syringe hepatitis." Liver damage has been observed most often with Aureomycin (chlortetracycline) but also occurs, to a lesser extent, with chloramphenicol and Terramycin (oxytetracycline). Fatty changes in the hepatic cells have been noted after the use of excessive quantities of Aureomycin, particularly when it is given intravenously.

tize individuals have been made and considered successful by some workers; however, such successes are open to the criticism that the patient may not actually have been seriously sensitized to the product used in the desensitization procedure or for subsequent treatment.

The antihistaminic drugs are of some value in the management of the acute delayed reactions of hypersensitivity, they sometimes give partial or complete relief from the pruritus associated with the skin lesions and may reduce the intensity or prevent the extension of the reaction, but they do not affect the arthrosis or lymphadenopathy. ACTH or cortisone relieve the itching and joint pains; they have little or no effect on anaphylactic phenomena.

Toxic and Irritative Reactions

Although they are at times difficult to separate from those related to sensitization, complications resulting from the direct irritating or toxic effects of various antibiotics are not uncommon. They are occasionally due to the use of excessive quantities or concentrations of a drug. In some instances, however, the antibiotic is variably but inherently toxic to certain tissues. These reactions may produce severe discomfort and rarely death.

Serious reactions involving the urinary tract have been observed following the administration of several of the antimicrobial drugs. Albuminuria and cylindruria are sometimes noted when streptomycin is administered, particularly when the urine is acid. A varying degree of renal decompensation may result from the administration of this drug, especially in individuals who have underlying kidney disease. The "broad-spectrum" antibiotics, Aureomycin (chlortetracycline), Terramycin (oxytetracycline), chloramphenicol, tetracycline (Achromycin, Tetracyn), penicillin and erythromycin are noninjurious to the kidney. The less commonly used antimicrobial agents such as bacitracin, polymyxin and neomycin are nephrotoxic in some but not all patients. Their

use may be accompanied by albuminuria, cylindruria, hematuria, and reduction in renal function which may be progressive, particularly in those with prior kidney damage. These changes are usually reversible if they are detected early and treatment is stopped; continuation of therapy in the face of increasing renal dysfunction may result in death.

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They do not occur when doses of 1 to 2 gm. a day are administered orally to patients or normal human subjects. That the toxic effect is related to dosage is strongly suggested by the reports of the beneficial effects of Aureomycin in acute hepatic disorders in which necrosis is prominent. It is very difficult, in many instances, to determine to what extent dietary disturbances and infection are responsible either directly for the hepatic changes or indirectly in conditioning the reaction of the liver to the antibiotic.

Mild anemia, hypochromic or normochromic, has been noted after prolonged chemotherapy; this may be unrelated to treatment, because it occurs frequently as a consequence of infection. The most serious blood disturbance produced by antibiotic agents is hypoplastic or aplastic anemia, which has occurred primarily following the administration of prolonged or repeated courses of chloramphenicol in doses which have not been excessive. It also occurs rarely with streptomycin. A number of deaths have resulted from this complication; some have followed the treatment of trivial conditions. In most instances, the first sign of trouble is the development of granulopenia; early recognition of the decrease in neutrophils followed by immediate cessation of therapy practically always leads to recovery of bone marrow function. The necessity for carrying out frequent blood counts in patients receiving chloramphenicol is obvious and cannot be overemphasized.

Several of the antibiotics produce nervous system disturbances. The intramuscular administration of concentrated solutions of antimicrobial agents may lead to their accidental introduction into peripheral nerves and the development of a chemical neuritis which may persist for a long time. Paresthesias of the hands, tongue, and circumoral areas have been caused by streptomycin but are particularly prominent with the use of polymyxin. The most frequent and serious of the neurologic disturbances provoked by antibiotic agents is damage to the eighth cranial nerve. The vestibular portion

of the nerve is injured most often by streptomycin while dihydrostreptomycin and neomycin affect the cochlear portion. The frequency and severity of the damage are directly related to the total quantity and duration of therapy. It has been suggested that the combination of equal quantities of streptomycin and dihydrostreptomycin (the total dose being no greater than when either agent is used alone) is effective in reducing the risk of auditory nerve injury; this has not been found to be true, however.

Considerable attention has been focused on the untoward effects of the intraspinal administration of antibiotics, particularly streptomycin and penicillin. Marked increase in intracranial pressure, hyperirritability, twitching, convulsions, coma, and death have been observed following the intrathecal instillation of these agents. The writer has not noted any complications of intraspinal chemotherapy in a large group of patients of varying age who have received a large number of injections. The majority of the severe reactions are probably the result of unintentional or accidental overdosage. The maximum quantity of penicillin which should be introduced intrathecally in adults in a single dose is 30,000 units and of streptomycin 100 mg. Smaller doses must be used in children. The observation of several other precautions aids in avoiding serious reactions: 1) The drug should be diluted in at least 10 ml. of physiologic saline; 2) the volume of spinal fluid withdrawn should be somewhat larger than that of the drug solution injected, and 3) the speed of injection should not exceed one ml. per minute.

A striking example of the highly irritating action af antibiotics is the thrombosis of veins which results from the intravenous administration of such agents as Aureomycin (chlortetracycline). The pain and muscle tenderness which follow the injection of large quantities of crystalline penicillin G and of other antibiotics are also due to irritation There is no conclusive evidence that any of the antibiotic agents, when given in the usual therapeutic doses, affects the

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tion of the bacterial population which normally inhabits certain tissues and organs. Such changes in microbial flora are most frequently of no clinical consequence, but occasionally are responsible for the superimposition of a serious infection on the one for which treatment was initially instituted. This is the phenomenon of *superinfection* which may be defined as the appearance of evidence (both bacteriologic and clinical) of a new infection at a time when the initial disease is responding clinically and bacteriologically to chemotherapy. Such secondary infections involve the respiratory tract, the colon, the genito-urinary tissues, and the middle ear most frequently. Acute enteritis due to *Staph. aureus* or "pseudomembranous colitis" in which *Proteus* and *Pseudomonas* predominate in the stool may follow the use of single drugs, particularly the "broad-spectrum" antibiotics, or preparation of the bowel for surgery by the administration of combinations of antimicrobial agents. The development of secondary pulmonary infections during treatment of bacterial or viral pneumonitis is not uncommon, particularly in young children. Chronic infection of the urinary tract which is responding to treatment may relapse while a drug is still being given; in such instances, bacteriologic study usually reveals an organism different from the one for which therapy was initially instituted and resistant to the antibiotic first applied. Among the complications occurring during chemotherapy is an overgrowth of yeasts and fungi in the mouth, pharynx, and intestinal tract. This is observed following the use of all of the antibiotic agents, but especially the "broad-spectrum" drugs. Mere increase in number of these organisms does not indicate, however, the presence of a superinfection. The significance of yeasts in lesions of the oropharynx and lung which appear during the administration of antimicrobial agents has been questioned. However, ulcerative stomatopharyngitis from which Monilia are isolated clear rapidly when gentian violet is applied locally, suggesting that these organisms are responsible for the disease. In some cases,

coagulability of blood. One of the mechanical difficulties that arises from the use of insoluble preparations of antimicrobial drugs follows their occasional accidental intravenous injection, with the development of diffuse pulmonary thrombosis. Such reactions are sometimes confused with anaphylactic episodes.

Biologic Alterations in the Host and Infecting Agent

Most of the antibiotic agents presently in clinical use are capable of producing biologic alterations in man and in the organisms which infect him. Some of these changes are of little consequence; others may seriously alter the course of the primary disease and occasionally may even be responsible for death.

Studies of the anti-metabolic effects of the antibiotic agents in human beings are few. Vitamin and other metabolic deficiencies have been described, many specific ones have been demonstrated in animals. In man, negative nitrogen balance and increase in riboflavin excretion result from the oral administration of moderate therapeutic doses of Aureomycin. Electrolyte disturbances occasionally accompany streptomycin therapy; they have been associated frequently with the use of viomycin, a tuberculostatic agent.

Urobilinogen may be absent from the urine and feces of patients during oral administration of Aureomycin (chlortetracycline) or Terramycin (oxytetracycline). This is probably due to suppression of the intestinal organisms responsible for the conversion of bilirubin to urobilinogen Bilirubin is present, however, in abundance in the stools and in normal quantities in the serum. The recognition of this chemotherapeutically-induced artifact is important in the differential diagnosis of hepatocellular disease and obstructive lesions in the biliary system.

The exhibition of an effective antibiotic to a patient with an infectious disease, in addition to eliminating the causative organisms, produces a profound alteration in the composi-

in prevalence of organisms resistant to most or all of the available antimicrobial agents. Many recent reports have stressed the importance of this problem, particularly in relation to *Staph. aureus.* While 75 to 85 per cent of strains of this organism were sensitive to penicillin 10 years ago, approximately the same percentage is at present resistant to this agent. Lack of drug-sensitivity in the *Staphylococcus* is not limited to penicillin; it is also becoming increasingly prominent with Aureomycin (chlortetracycline), Terramycin (oxytetracycline), chloramphenicol, tetracycline and erythromycin. It must be pointed out, however, that the marked increase in antibiotic-insensitive staphylococci is most prominent in hospitalized patients. In the general population, the incidence of penicillin-resistant strains is only about 10 per cent. The *Staphylococcus is* not the only organism which has become insusceptible to antibiotics. Many of the gram-negative bacteria responsible for urinary tract infections, *E. coli, Ps. pyocyaneus, A. aerogenes,* and *Proteus,* for example, are developing decreased sensitivity to various chemotherapeutic agents, and infections due to them are becoming increasingly more difficult to manage. The phenomenon of emergence of drug resistance is not common to all bacterial or all antibiotic agents. It is a fortunate circumstance indeed that, despite their long exposure, the organisms responsible for some of the common infectious diseases have remained highly susceptible to antimicrobial drugs. There are, for example, no authenticated strains of penicillin-resistant *Pneumococcus, Gonococcus,* or beta-hemolytic *Streptococcus.*

Treatment with antibiotics may depress the formation of antibodies to various organisms and their products. It has been demonstrated, for example, that prompt and intensive penicillin therapy of acute streptococcal infections of the respiratory tract inhibits the elaboration of antistreptolysin, antistreptokinase and type-specific antibacterial antibody. In pneumococcal infections in man, on the other hand, penicil-

diffuse fungus infection develops, the central nervous system, kidneys and other viscera are invaded, and death results. There is, at present, no effective treatment for disseminated moniliasis or most of the other diffuse mycoses.

Although the problem of superinfection has been recognized for a long time, it has always been considered to be an uncommon and even rare phenomenon, and very little has been known concerning the factors which predispose to its development. A recent study of 3095 patients who had received one or another antibiotic agent revealed the incidence of superinfection to be 2.19 per cent. Secondary infections most often involved the tissue which was the original site of disease, although other organs were occasionally affected. They appeared most frequently about 4 to 5 days after antimicrobial therapy was instituted. The individuals most susceptible were those who were less than 3 years of age, those whose primary disease was in the lungs, and those who received drugs with relatively "broad" antimicrobial effect, particularly combinations of agents. In most cases, more than one factor was involved; the more numerous the predisposing situations, the greater was the risk of secondary disease. Antibiotic-produced infections occasionally convert a benign and self-limited disease into a serious, prolonged, or even fatal one. This is, in part, due to the fact that the responsible organisms, *Proteus, Pseudomonas,* drug insensitive staphylococci, and yeasts for example, are not very susceptible or are totally resistant to the available antibiotic agents.

Abscesses sometimes develop at the site of injection of antibiotics. They are usually due to organisms resistant to the drug which produced them. *E. coli, P. vulgaris* and *Cl. perfringens* (B. welchii) have been isolated from such lesions. The source of these bacteria may be the skin, the antibiotic, or improperly sterilized needles and syringes.

Potentially one of the most serious complications of the widespread use of antibiotics is the emergence and increase

The infectious disease in which combined chemotherapy is most effective is tuberculosis. Combination of para-aminosalicylic acid or isonicotinic acid hydrazide and streptomycin is more effective in pulmonary tuberculosis than streptomycin alone. In some of the bacterial meningitides other than tuberculous, combined chemotherapy is also more effective than single agents. Thus, although streptomycin alone, given intrathecally and intramuscularly, is quite effective in the management of many cases of *H. influenzae* meningitis, the simultaneous use of sulfadiazine increases the number of recoveries and decreases the incidence of bacterial resistance. Pneumococcal meningitis is thought by some investigators to be best treated by the simultaneous administration of penicillin and sulfadiazine.

There is clinical support for the use of combined therapy in some infectious diseases. In other situations, however, combinations of antibacterial substances are used because (1) satisfactory results are not obtained with a single drug, (2) multiple organisms are present, or (3) the causative agents have not or cannot be isolated. In general, the use of combinations of antibiotic agents cannot be recommended for the treatment of infection until more clinical evidence becomes available to validate their effectiveness. The disadvantages of this type of therapy are (1) inability to "tailor" a combination which will be effective in all cases at the dosage level used, (2) the increased danger of allergic reactions from the use of multiple agents, and (3) a greater risk of superinfection.

Misuses of Chemotherapy

It is impossible in a limited space to discuss in detail all the misuses of the antibiotics. There is little doubt that these drugs are often employed in many situations where they are not required, and that even when they are indicated, a poor clinical result follows failure to administer them properly.

lin treatment produces no detectable alteration in the serologic response. The use of Aureomycin (chlortetracycline), Terramycin (oxytetracycline), or chloramphenicol in scrub typhus produces no appreciable effect on the eventual height of the titer of OX-K antibodies. If treatment is started early in the disease, the appearance of agglutinins may be somewhat delayed.

Combinations of Chemotherapeutic Agents

There is some evidence to suggest that the simultaneous administration of two or more antibacterial agents may be more effective in certain infections than the same drugs used individually in equal or larger amounts. True synergistic effects are only rarely derived from combinations of various chemotherapeutic substances. Increased activity is usually an additive effect. With some combinations no change in antibacterial potency occurs. With others, one agent may, to a varying degree, inactivate the effectiveness of the other.

There are a few chemotherapeutic combinations of proved value in clinical medicine. In the management of cases of subacute bacterial endocarditis due to strains of *Streptococcus viridans* and enterococci which are relatively unresponsive to penicillin, the addition of streptomycin (2 to 4 gms. per day) may be helpful in eradicating the organisms from the blood stream and effecting clinical cure. In general, brucellosis responds better to various combinations of drugs than to single agents. Although both Aureomycin and Chloromycetin are known to produce good immediate clinical results in brucellosis, the simultaneous administration of streptomycin and Aureomycin produces more rapid cure and decreases the incidence of recurrence. Erythromycin in combination with chloramphenicol, streptomycin or bacitracin may be of great value in the treatment of systemic infections due to *Staphylococcus aureus*.

focus, chemotherapy may be delayed until adequate clinical and laboratory studies have been carried out. *Fever is not in itself a good reason for plunging into the use of the antibacterial drugs.* Considerable thought and judgment must be exercised before resorting to chemotherapy as a diagnostic-therapeutic measure.

Serum Therapy

The development of effective chemotherapeutic agents for many of the important infectious diseases has greatly reduced the necessity for the use of serum therapy. There is, for example, no need for the administration of specific antiserum in pneumococcal, meningococcal, and *H. influenzae* infections or in scarlet fever. The situations in which serotherapy is still useful and, in some instances, represents the most efficient method of treatment include snake bites, tetanus, gas gangrene, diphtheria, botulism, and possibly pertussis. The serums used for therapeutic purposes are mainly derived from animals which have been immunized by repeated injection of the specific antigens. Antipertussis antibody is obtained from humans who have had this disease and have subsequently been subjected to artificial active immunization. The quantities of serum used in therapy are considerably larger than those employed in the prophylaxis of an infection or intoxication and are doubtless in excess of those actually necessary; the quantitative aspects of this type of treatment are more or less empiric. The details regarding dosage of serum in specific infections are discussed elsewhere in this book. The principles governing the excretion of therapeutically applied antibody are the same as those that pertain when the material is given prophylactically.

Heterologous serums must under no circumstances be injected until tests for hypersensitivity have been carried out. The instillation of 0.1 ml. endermally or into the conjunctival

Listed below are the most common misuses of the chemotherapeutic agents.

1. Treatment of obscure fever.
2. Choice of ineffective antibiotic.
3. Inadequate or excessive doses.
4. Use in insusceptible infections—measles, mumps, varicella, poliomyelitis, rheumatic fever, influenza, herpes simplex, herpes zoster, viral influenza, and undefined upper respiratory tract infections.
5. Improper route of administration—failure to use drugs locally, in pleural or joint spaces, for example: application to the skin in ointment form, because of the high incidence of sensitization.
6. Continuation of therapy with a drug to which bacterial resistance has developed.
7. Failure to alter type of chemotherapy when superimposed infections with insensitive organisms occur.
8. Failure to stop treatment in presence of a serious toxic or allergic reaction.
9. Prophylaxis of minor respiratory tract infections.
10. Use of sulfonamides in prevention of wound infections.
11. Use of improper combinations of chemotherapeutic agents.
12. Reliance on chemotherapy or prophylaxis to the exclusion of necessary surgical intervention, e.g., drainage of localized areas of infection.

Probably the most frequent chemotherapeutic misuse arises from the treatment of fever of obscure origin. The mere presence of fever, in the absence of localizing signs, does not necessarily indicate that the temperature elevation is due to an infectious disease (Chapter *XVII*). In the absence of strong clinical evidence that a febrile episode is infectious in origin, particularly when there is no detectable

Reactions to the Administration of Serum: In spite of careful sensitivity testing, severe sequelae may develop in patients who, by all tests, appear not to be allergic to serum. Such reactions may occur at 3 different intervals after injection and be of several clinical types. The first and most serious is anaphylaxis: this usually supervenes within a few seconds to minutes after inoculation. It may lead to instantaneous death without any demonstrable signs or symptoms; this is, fortunately, very rare. More often, itching, an urticarial eruption, dyspnea, cough, wheezing, chest or abdominal pain, nausea, vomiting, marked hypotension, syncope, or collapse, in any combination, are observed. If treated promptly with epinephrine, most cases survive. The second type of reaction appears 2 to 5 days after giving serum and has been called the "anaphylactoid" reaction or "accelerated serum sickness." Its features are quite like those of ordinary serum sickness; it is differentiated mainly by the fact that it appears relatively early. Classic serum sickness occurs in from 10 to 14 days after the injection of serum. The incidence of this sequel is roughly related to the quantity of serum administered; if 10 ml. or less are injected, it is about 10 per cent, while with 75 ml. or more, it is increased to about 75 per cent. Treatment of heterologous serums with acid or proteolytic enzymes "despeciates" them and reduces, but does not completely eliminate, the risk of serum sickness The clinical syndromes which appear differ markedly in severity and extent but consist of one or more or all of the following features: fever, generalized aching, arthralgia or arthritis, maculo-papular eruptions, urticaria, diarrhea, abdominal pain, generalized lymphadenopathy, hypotension, periorbital edema, and various signs and symptoms of nervous system dysfunction. As a rule, all of the manifestations clear in 3 to 5 days and leave no residua. Rarely, serious or fatal complications may occur; these include myocarditis, meningitis, meningo-encephalitis, myelitis with or without encephalitis, and peripheral neuritis. Myocarditis may be

sac and observation for local reactions after 20 to 30 minutes usually suffices to determine sensitivity. A careful inquiry into the presence of any type of allergic disease in the present or past is also of great importance. In most adults, even in the absence of a positive history or a reaction in the skin or eye, it probably is safest to give a small initial dose of serum and, if no untoward effects are noted after 30 minutes, to administer the remainder in 4 or 5 equal portions at half-hourly intervals. In patients who require serotherapy but are sensitive to the material being used, "desensitization" must be carried out. This is accomplished by starting treatment with a very minute amount (as little as 0.1 ml. of a *1:100,000 dilution* may be *necessary*) and *increasing it* every 20 to 30 minutes until the required quantity has been given. *Serum of any kind must never be administered unless a syringe full of 1:1000 dilution of epinephrine solution is close at hand and ready for use.*

One of the most important features of serotherapy, particularly as it applies to the management of disease due to bacterial toxins, is the fact that once exotoxins are fixed to tissues they cannot be inactivated by specific antiserum, regardless of the quantity given. This phenomenon emphasizes the futility of trying to alter the clinical changes already present at the time antitoxin is given. The primary purpose and effect of serotherapy, therefore, is to neutralize the toxic materials still free in the blood and tissue fluids, and to provide a pool of protective antibody for inactivation of any more toxin that may be formed at the site of infection.

The site of choice for inoculation of antiserums is intramuscular. *For prophylactic purposes this is adequate. When* serum is used therapeutically, however, it is necessary to produce a *high level of antibody in the blood rapidly. For* this purpose, it is best to administer about 50 per cent of the required dose of serum intramuscularly, and, if no reaction occurs in an hour or more, to give the remainder intravenously.

CHAPTER III

PRINCIPLES OF PREVENTION OF INFECTION

Non-Specific Prophylaxis

The spread of bacterial and viral diseases can be prevented to some extent by the application of non-specific methods. For example, reduction of overcrowding slows appreciably the dissemination of respiratory and gastro-intestinal infections. Proper application of asepsis in surgical procedures, in preparation of parenterally administered drugs, in handling of wounds, and in injection of various sterile materials has become a commonplace. The wearing of face masks, although not completely effective, is of some help in decreasing the risk of transmission of invasive agents in respiratory poliomyelitis or tuberculosis. The purpose of isolation and quarantine of patients and the boiling of dishes, and careful handling of everything with which they come in contact is to minimize the danger of cross infection. The degree of contamination of the environment by pathogenic organisms may be reduced by the use of ultraviolet irradiation or spraying with propylene glycol, in special circumstances. Passing of bed clothes through a soap-oil mixture which leaves a very thin film of oil on the cloth in the final stage of laundering has been shown to decrease the spread of streptococci in the hospital. The control of carriers is very important in preventing most enteric infections. The proper handling of potentially contaminated food, water, or animals and their products, as well as boiling of water, pasteurization of milk, and adequate cooking of meat are important prophylactic measures. The eradication or immunization of vectors of

detected more frequently than it is suspected clinically if serial electrocardiographic studies are carried out. Any single division or the entire nervous system may become involved; although the incidence of this accident in serotherapy is very low, the death rate is of the order of 15 to 20 per cent. The clinical pictures are characterized by their variability. The cerebrospinal fluid usually contains an increased number of cells and quantity of protein. In spite of occasional reactions, even serious ones, there must be no hesitancy in administering specific antiserum in situations where it is required. Chemotherapy has not solved many of the problems in the field of infectious disease; although antibiotics have a definite place, the only truly effective therapeutic measure in diseases like diphtheria, tetanus, snake bite, botulism, and gas gangrene is still highly potent antitoxin.

ACTIVE IMMUNOLOGIC PROPHYLAXIS

Active immunologic prophylaxis is usually produced by the injection of dead or living viruses or bacteria or their products. When viable agents are used, immunity is usually prolonged and needs to be renewed only at long intervals; in some instances, a single administration produces protection for life. With vaccines consisting of dead bacteria or toxoid, the duration of the protective effect is variable, but, as a rule, periodic "booster" doses are required to maintain the constant presence of a protective level of antibody. The duration of immunity is briefest when killed virus is

TABLE 2

ACTIVE IMMUNOLOGIC PROPHYLAXIS

Disease	*Agent Used for Prophylaxis*
Pneumococcal pneumonia	Type specific bacterial polysaccharide
Typhoid Fever	Killed bacterial suspension
Salmonella—Paratyphoid A and B	Killed bacterial suspension
Pertussis	Killed bacterial suspension
Cholera	Killed bacterial suspension
Plague	Killed bacterial suspension or special avirulent strain of living organisms
Tularemia	Killed bacterial vaccine
Tuberculosis	Attenuated bovine tubercle bacillus—BCG
Diphtheria	Alum or formalin treated toxoid
Tetanus	Alum or formalin treated toxoid
Rabies	Formalin—killed virus in rabbit spinal cord
Mumps	Formalin—killed virus
Influenza	Killed virus
Poliomyelitis	Formalin—killed virus
Yellow Fever	Living attenuated virus
Smallpox	*Live vaccinia virus*
Rocky Mountain Spotted Fever	Killed rickettsia
Epidemic Typhus Fever	Formalin treated infected chicken egg yolk sac tissue

infectious agents is another non-specific method of decreasing the risk of infection in man. The application of DDT in typhus endemic or epidemic areas and spraying with oil or DDT to kill Anophelene species of mosquitos reduce sharply the incidence and prevalence of typhus fever and malaria respectively. The elimination of ticks by burning or chemical agents may keep tularemia or Rock Mountain Spotted Fever from becoming widespread in an area.

Passive Immunologic Prophylaxis

Passive immunologic prophylaxis is usually produced by the administration of animal or human serum, or gamma globulin which contains potent antibody for a specific infectious agent. As a rule, this type of protection is of short duration; it is used when no other method is available or when the period between contact and the appearance of disease (the incubation period) is too short to allow active immunization. When heterologous serum is given, the period of prophylaxis lasts for approximately 2 weeks; with human serum or gamma globulin, it is maintained for about 4 to 5 weeks. The diseases for which this type of prophylaxis is available and the materials used are listed in Table 1.

TABLE 1

PASSIVE IMMUNOLOGIC PROPHYLAXIS

Disease	*Agent Used for Prophylaxis*
Tetanus	Horse serum antitoxin
Gas Gangrene	Polyvalent horse serum antitoxin
Diphtheria	Horse or bovine serum antitoxin
Botulism	Horse serum antitoxin
Pertussis	Human hyperimmune serum or gamma globulin
Measles	Normal human gamma globulin
Infectious Hepatitis	Normal human gamma globulin
Poliomyelitis	Normal human gamma globulin
Rabies	Hyperimmune rabies horse serum
Mumps	Hyperimmune human serum
Rubella	Immune human serum

Chemoprophylaxis in Healthy Individuals

Chemoprophylaxis is most commonly employed in healthy individuals to prevent invasion by specific bacteria. It may be given either to single patients, to families, or to large groups of people, some of whom have not yet had contact with an organism and others of whom are already harboring it as asymptomatic carriers. This type of prophylaxis is most successful in protecting against infection by four agents—the beta-hemolytic streptococcus, the gonococcus, the meningococcus and the dysentery bacilli. The details of the use of drugs in the prevention of these diseases are presented in the chapters in which they are discussed.

Chemoprophylaxis in Acutely Ill Individuals

The antimicrobial agents have been used extensively for the prevention of bacterial invasion in individuals taken suddenly ill with disorders in which these drugs have no therapeutic effect. The primary diseases in which such chemoprophylaxis has been employed are of two types: (1) those due to various viruses, and (2) those which are non-infectious in origin.

One of the most common prophylactic uses of the antibiotics is in undefined viral disease of the upper respiratory tract. Attempts to prevent secondary infections following the "common cold," while most desirable, have not proved very successful. Although it has been the impression of some clinicians that benefit was derived from such prophylaxis, this is not based on studies of large groups of patients with an adequate number of untreated controls. Depending on the antimicrobial agent used, certain pathogenic bacteria may be prevented from producing disease in the person with a viral respiratory infection. However, regardless of the prophylactic program employed, invasion by all organisms cannot be eliminated. For this reason the etiology of the complications may be altered by chemoprophylaxis, but

used, usually one year or less. In Table 2 are listed the common infections in which active immunization may be carried out and the agents which are employed for this purpose.

Chemoprophylaxis of Infection

The effectiveness of the antimicrobial agents in eliminating certain bacteria and in curing the diseases produced by them has led to their use for the prevention of specific infectious processes, or of infection in general; this application of the antibiotics and sulfonamides constitutes *chemoprophylaxis*. The results obtained when drugs have been employed for this purpose have been quite variable. In some instances, chemoprophylaxis has been eminently successful; in others it has failed completely, while in still others no conclusion can be reached because of the inadequacies of the available data.

Chemoprophylaxis has been used primarily for four purposes: (1) to protect healthy individuals, either singly or in groups, against invasion by specific microorganisms; (2) to prevent secondary bacterial infection in people acutely ill with diseases for which the antimicrobial agents are not effective; (3) to reduce the risk of infection in patients with various types of chronic illness; and (4) to inhibit the spread of disease from areas of localized infection, or to prevent infection in general, in persons who have been subjected to accidental or surgical trauma. The degree of success has varied with the purpose for which prophylaxis has been applied; it has been highest when the prevention of specific infections has been attempted, and lowest when protection against infection in general has been its aim. In many instances, prophylactic measures have been applied only to single individuals; in others, they have been used for large groups. In many cases, chemoprophylaxis, whether effective or not, has resulted in no untoward reactions; in some, it has converted a benign, self-limited disease into a serious or even life-threatening one.

neys, or both. The sulfonamides, usually in a dose of 2 gm. a day, have been used for a long time for prophylaxis in this situation. The results have been variable. Their use, in the usual quantities, is often without benefit in the face of constant catheter drainage. The administration of other antibiotic agents has not significantly altered the situation. Two other approaches to this problem are possible. The first is tidal drainage; this reduces, to some degree, the risk of infection. The other involves increasing the dose of the antimicrobial agent to full therapeutic levels for at least one week after removal of the catheter, because the quantities of drug used for prophylaxis frequently do not prevent bacteria from being present in appreciable numbers, despite absence of active infection. With cessation of treatment, the organisms often multiply and invade the tissues The administration of large doses of a chemotherapeutic agent may eliminate the bacteria before they produce disease. It is of great importance to emphasize the necessity of encouraging a patient to void before catheterization is resorted to. In many instances, urinary retention is acute in onset and short in duration, and with patience and proper management the insertion of a tube into the bladder may not be necessary. One of the most effective ways to prevent urinary tract infection is to avoid, wherever possible, the use of the catheter.

On the whole, chemoprophylaxis in patients with acute diseases for which antimicrobial agents are not effective is not very successful. Since, in addition, there is always the risk of superinfection and other reactions, some of which may be serious, the use of antibiotics to prevent secondary infections in the conditions just discussed may not be justifiable, except in unusual circumstances.

Chemoprophylaxis in Chronic Disease

While not all individuals who have had rheumatic fever have residual valvular defects, their susceptibility to new

their incidence is very little, if at all, changed. There is considerable question whether prophylaxis should be given in "primary atypical pneumonia" or some of the other undefined viral pneumonitides, since secondary bacterial infection in untreated cases is uncommon. In viral influenza, the risk of superimposed bacterial disease is greater than in the undefined viral pneumonias, and chemoprophylaxis may, therefore, have more justification. It is important to emphasize, however, that complicating infections by bacteria cannot be completely avoided and that, when they occur, they may be very serious and caused by *Proteus* or *Staph. aureus* or other organisms relatively difficult to eliminate.

Antibiotics have often been administered in the so-called "childhood diseases" to prevent secondary bacterial infection. There is no evidence that they are of any benefit in this regard when given in cases of measles, chicken pox, or mumps Failure of antimicrobial agents to protect against bacterial invasion in "respiratory" poliomyelitis is very common. Attempts to prevent superimposed bacterial infections in pertussis have been disappointing

It is common practice to administer antibiotic agents to patients with heart failure, coma due to various causes, cerebrovascular accidents, or shock for the purpose of preventing bacterial infections. Despite the wide use of such prophylaxis and the general impression that it is effective, little or no conclusive evidence has been obtained from controlled observation to substantiate its usefulness. Since individuals with these conditions are quite susceptible to bacterial invasion, they are exposed to the risk of superinfection even if they receive antibiotics.

The necessity to catheterize the urinary bladder usually arises as an acute situation. Although single catheterizations are attended by a certain risk of infection of the lower urinary tract, the presence of an indwelling tube is almost certain to result in bacterial invasion of the bladder or kid-

episodes of the acute rheumatic state and the risk of cardiac damage make it imperative that everyone who has recovered from this disease be protected against infection by the beta-hemolytic streptococcus, which is responsible in most instances for recurrences. The two agents which have been used most extensively for the prevention of rheumatic fever are sulfadiazine and penicillin. The administration of 1 gm. of sulfadiazine per day has been found to reduce the recurrence rate by 85%; the incidence of reactions with this drug is low (0.1% mild and 0.01% severe). Both parenteral and oral preparations of penicillin have been employed for the same purpose. Very satisfactory results have been noted with this antibiotic; in some groups, recurrence of rheumatic fever has been entirely eliminated. One of the problems which still remains to be resolved in the use of penicillin is establishment of the optimal dose. Quantities ranging from 100,000 units twice a day to 200,000 units three times a day have been given by mouth, with success. A single intramuscular injection of 600,000 units [illegible] lin) once a month [illegible] recently been suggested that [illegible] be continued throughout the entire life of the patient.

It has been estimated that about 25 per cent of cases of subacute bacterial endocarditis follow dental extraction. The fact that transient bacteremia occurs in from 20 to 60 per cent of persons who have teeth removed has emphasized the importance of chemoprophylaxis in patients with acquired or congenital heart disease. Penicillin is the agent of choice for this purpose. The following schedule is recommended: 250,000 units of buffered penicillin G every 6

hours by mouth for 2 days prior to operation; on the day on which the extraction is performed, the same dose of drug is given by mouth, but, in addition, 1,000,000 units of procaine penicillin is injected intramuscularly just prior to surgery. Oral penicillin administration is continued for the 2 days after extraction.

Patients with chronic bronchitis, emphysema, and bronchiectasis are highly susceptible to superimposed bacterial infections. It has been reported that the administration of 0.5 gm. of chloramphenicol daily to individuals with these disorders resulted in a reduction in respiratory infections of 50 per cent.

Children with cystic fibrosis of the pancreas (mucoviscidosis) are particularly susceptible to infections of the lung, especially by *Staph. aureus*. For this reason, chlortetracycline (Aureomycin) has been given prophylactically. Although staphylococci can often be cultured from the respiratory tract of these patients while they are receiving antibiotic, the risk of repeated episodes of pneumonia is sharply reduced, and life is prolonged and made much more comfortable.

Chemoprophylaxis of Surgical or Accidental Trauma

One of the most common areas of use of chemoprophylactic agents has been in elective surgery. The purpose of this has been to prevent postoperative pulmonary and other infections. Although it is the general impression that the administration of antimicrobial agents results in a reduction in the incidence of postoperative infectious complications, this is not true. Infection of clean wounds takes place after operation despite the prophylactic use of antibiotics, may become a serious problem, and is usually due to invasion by strains of *Staph. aureus*, which are resistant to penicillin and other antibiotics There is no evidence that the incidence

of postoperative pneumonia is decreased by chemoprophylaxis.

Antibiotics in various combinations have been used extensively for preparation of the bowel for surgery. The agents which have been employed most widely for this purpose have been the so-called "broad spectrum" antibiotics. Although the number of organisms in the intestine may be markedly reduced, complete sterilization has rarely, if ever, been accomplished. Pseudomembranous colitis or acute staphylococcal enteritis (either of which may be fatal) occasionally appears during the course of antibiotic preparation of the intestine for surgery.

Surgical treatment of infected areas, such as the tuberculous lung, localized abscesses, bronchiectasis and others, is an indication for the use of chemoprophylaxis prior to and after operation. In this type of surgery the administration of antimicrobial agents appears justified even in the face of the risks which may be involved. The type of drug employed must be determined by the location and etiology of the infection. In accidental wounds or burns, chemoprophylaxis has not been very successful. The administration of penicillin to patients with burns does not prevent infection by staphylococci resistant to this agent or by gram-negative bacteria difficult to eradicate with antimicrobial drugs. Infection is not completely prevented even when combinations of antibiotics are given, in these instances, the organisms involved are frequently *Proteus* or *Pseudomonas*. Sulfonamide powder is ineffective prophylaxis.

In obstetrical practice, patients with prolonged and difficult labor are susceptible to puerperal infection, and the use of an antibiotic to prevent this complication may be justified. On the other hand, the general application of chemoprophylaxis to all women after completion of labor requires substantiation of its necessity. Careful studies, including an adequate number of untreated controls to prove the effectiveness of this type of prophylaxis, remain to be carried out.

Dangers of Chemoprophylaxis

The same untoward effects which occur when antibiotic agents are used for therapeutic purposes are observed when patients who have no active infection are given these drugs. Thus, allergic episodes varying in severity from mild skin rashes to fatal attacks of acute anaphylaxis, a variety of reactions due to the irritating and toxic properties of the antimicrobial agents, disturbances in metabolism, and serious superinfections have occurred in individuals who have been given antibiotics for the prevention of bacterial invasion. The risk of the development of reactions and the difficulties which they involve must always be taken into consideration in planning a program of chemoprophylaxis. In instances where the use of antibiotic agents for protection against infection is of proven value, taking the risk is completely justified. In cases where the effectiveness of prophylaxis is questionable, the situation must be carefully scrutinized before treatment is started, and the benefits to be derived must be weighed against the possible dangers. When there is no evidence that chemoprophylaxis will be effective, it *should not be given.*

CHAPTER IV

INFECTIONS OF THE MOUTH AND SALIVARY GLANDS

INFECTIONS OF THE TONGUE

The tongue is not infrequently involved in disorders in which the primary lesions are not in the mouth. For example, lingual changes occur in scarlet fever (strawberry and raspberry tongue) and after the use of antibiotics (black, brown or "furred" tongue). Syphilis may produce an atophic glossitis, bald tongue, or gumma; primary chancre of the tongue is rare, but mucous patches characteristic of the secondary stage of lues are quite common. Ulceration of the tongue is rarely due to tuberculosis. Diffuse monilial stomatitis in adults or thrush in infants is characterized by typical shallow ulcerations covered by white, heaped-up exudate on the tongue. Many cases of acute glossitis, with complete loss of the lingual epithelium observed during the course of various infections, are not the result of the infectious process itself but arise because of direct irritating effects of, or sensitization to, the drugs used for therapy.

INFECTIONS OF THE LIPS

The commonest infection of the lips is herpes simplex or "fever blisters" (herpes labialis). After primary contact with the herpes virus, the organism takes up residence at the mucocutaneous borders where it lives in complete symbiosis with the host. No disease results until something occurs to disturb this symbiotic relationship. Fever is thought to be the common denominator; herpes simplex of the lips is more

common after pneumococcal and meningococcal infections than after invasion by other organisms. Sunburn may also produce herpes labialis. The "fever blister" usually starts with a sensation of slight itching or pain at the site of its subsequent appearance. Within a very short time, a group of vesicles appear at the mucocutaneous border; these rupture easily and become covered with a brown crust. Fever and constitutional reaction are not present. The diagnosis is readily established on the basis of the appearance of the lesions; specific proof is obtained by demonstration of an increase in neutralizing antibody for herpes virus in the patient's serum. There is no specific therapy for this infection. It usually heals very rapidly. Encephalitis is a rare complication.

Infections of the Mouth

A number of the infectious diseases in which changes appear in the buccal mucous membrane are discussed in various chapters of this book. Special comment must be made, however, concerning the differential diagnosis of vesicular and bullous lesions of the mouth because these are very common. They are observed in Coxsackie disease, erythema multiforme exsudativum, herpes simplex infection, one form of infantile viral diarrhea, pemphigus, and sensitization to various drugs. The etiology of these is usually detectable on the basis of the characteristic clinical features of the disease or the presence of signs indicating involvement of other systems. There remains, however, a group of conditions collectively called "aphthous stomatitis." The etiology of these lesions is unknown in most cases. The term "aphthous stomatitis" is often a wastebasket into which is thrown all idiopathic vesicular lesions of the oral mucous membrane; it is an anatomical and not an etiologic diagnosis. Other than the application of soothing medications and physiologic salt solution irrigations, there is no therapy for this condition.

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common after pneumococcal and meningococcal infections than after invasion by other organisms. Sunburn may also produce herpes labialis. The "fever blister" usually starts with a sensation of slight itching or pain at the site of its subsequent appearance. Within a very short time, a group of vesicles appear at the mucocutaneous border; these rupture easily and become covered with a brown crust. Fever and constitutional reaction are not present. The diagnosis is readily established on the basis of the appearance of the lesions; specific proof is obtained by demonstration of an increase in neutralizing antibody for herpes virus in the patient's serum. There is no specific therapy for this infection. It usually heals very rapidly. Encephalitis is a rare complication.

Infections of the Mouth

A number of the infectious diseases in which changes appear in the buccal mucous membrane are discussed in various chapters of this book. Special comment must be made, however, concerning the differential diagnosis of vesicular and bullous lesions of the mouth because these are very common. They are observed in Coxsackie disease, erythema multiforme exsudativum, herpes simplex infection, one form of infantile viral diarrhea, pemphigus, and sensitization to various drugs. The etiology of these is usually detectable on the basis of the characteristic clinical features of the disease or the presence of signs indicating involvement of other systems. There remains, however, a group of conditions collectively called "aphthous stomatitis." The etiology of these lesions is unknown in most cases. The term "aphthous stomatitis" is often a wastebasket into which is thrown all idiopathic vesicular lesions of the oral mucous membrane; it is an anatomical and not an etiologic diagnosis. Other than the application of soothing medications and physiologic salt solution irrigations, there is no therapy for this condition.

Fusospirochetal Gingivitis

Under certain conditions, the fusiform bacilli and spirochetes normally present in the mouth may invade and produce severe gingivitis ("trench mouth"). As a rule, one or more predisposing conditions, local or systemic, are present. Deposits of "tartar," injuries to the gums, and burns of the mouth are among the local conditions which set the stage for the infection. Chronic debilitating disease, nutritional deficiencies, or other situations may also be important factors.

The manifestations of fusospirochetal gingivitis vary in intensity. In the very mild cases, there are no symptoms; the free edges of the gums are reddened and somewhat swollen, and may bleed freely on brushing the teeth. In severe infections, the gingivae are painful, tender, and markedly swollen, and the crevices are filled with gray, cheesy, foul-smelling exudate. There is marked fetor oris. Fever and leucocytosis may be present.

The diagnosis is made on the basis of the appearance of the gums and the demonstration by stained smears of large numbers of fusiform bacilli and spirochetes in the gingival exudate. All patients should be studied for evidence of local or systemic disease. In mild infections, the removal of calcareous deposits around the teeth, frequent irrigation of the mouth with *dilute* sodium perborate solution, and good dental hygiene are often sufficient to cure the disease and prevent recurrence. In addition, severe cases require the administration of antibiotics; 600,000 units of procaine penicillin daily, or tetracycline (0 25 gm. every 6 hours orally) given for 10 to 12 days are usually effective. Uncommon but *serious complications* of untreated fusospirochetal gingivitis are Vincent's angina (Chapter VI), gangrene of the lungs (Chapter VII), or vulvovaginitis or balanitis (Chapter XII).

Infective Gangrene of the Mouth (Cancrum Oris)

Gangrene of the mouth occurs mainly in children who have been on a protein-deficient diet for an appreciable period of time. The onset of the oral lesion is usually preceded by fetor oris and increased salivation for 1 to 2 weeks. This is followed by swelling of the mouth, fever, and ulceration of the gum margin. The course of the infection may be divided into two phases. The first stage is characterized by tender firm swelling of the affected part of the maxilla or mandible which varies in size from a few centimeters to a huge mass, severe gingivitis, marked malodorous breath, and swelling of the overlying part of the face. The teeth near the center of the infected area become loosened early because of extension of infection into the bone. About 50 per cent of patients have superficial ulceration of the adjacent cheek. If treatment is not undertaken at this time, the second stage of the disease appears. In this phase, there is usually fully developed gangrene, extensive gingivitis, a varying degree of osseous necrosis, and a lesion of the flush areas of the face. Infection is usually present on the inner surface of the cheek opposite the maximal area of bone involvement. The tissues have a tan, brawny deep red appearance at first which always progresses to actual gangrene despite therapy. The gangrenous area is sharply demarcated and surrounded by a yellow leathery rim. After a few days, the affected tissues become loosened and slowly slough away leaving a cavity of varying size. Most patients in this phase of the disease appear very ill, are badly malnourished, and have some degree of hepatosplenomegaly. Moderate or marked intermittent fever is relatively common, and a slight polymorphonuclear leucocytosis is usual.

The etiology of gangrene of the mouth is not clear. Most lesions reveal fusiform bacilli and spirochetes similar to those responsible for Vincent's angina; these are usually present

together with a variable mixture of other bacteria. Invasion by these organisms is thought to be related to nutritional deficiency. It has been suggested that after a prolonged period of general malnutrition, particularly in protein and vitamin B, fusospirochetal gingivitis develops. In many instances, the process does not progress beyond this point. In badly malnourished individuals, however, it spreads along the roots of the teeth, involves the jaw, and produces bone necrosis. The infection may halt at this time, but, in some cases, it spreads rapidly to the adjacent soft tissues by direct contact and results in gangrene of the inner surface of the cheek which advances peripherally, involving the entire thickness of the soft tissues.

The diagnosis of infective gangrene of the mouth is made on the basis of the clinical appearance and the course of the infection. It is confirmed by the evidence of malnutrition in the patient and the demonstration of fusiform bacilli and spirochetes in the lesion. The bacteria are best visualized by gram-stained smears of exudate; they are very difficult to culture since they are very strictly anaerobic. Treatment consists of intramuscular injection of 600,000 to 1,000,000 units of procaine penicillin per day, and is continued until all necrotic material has sloughed away and a clean area remains; in some cases, this may require 2 months. Good results may also be obtained with the oral administration of 75 to 100 mg. of chlortetracycline (Aureomycin) per Kg. of body weight per day. A diet high in protein and members of the vitamin B complex must also be given.

Another form of gangrene involving mainly the tissues at the angles of lips, face, buccal mucous membrane, and mucocutaneous borders occurs after bites or other accidental injuries of the mouth in normal individuals. This is usually due to implantation of organisms normally present in the oral cavity, primarily fusiform bacilli and spirochetes. The involvement of the buccal mucous membrane, lips, and cheek may progress very rapidly producing extensive gangrene and

loss of tissue. If the disease is not recognized and treated promptly, secondary infection and death may take place. The diagnosis of this type of infection is based on a history of injury to the inner surface of the mouth or lip, the presence of the typical destructive lesion, and the demonstration in gram-stained smears of a preponderance of spirochetes and fusiform bacilli. Treatment is the same as that for infective gangrene of the mouth.

Ludwig's Angina

Primary Ludwig's angina frequently starts with slight pharyngeal inflammation which usually disappears in a day. This is followed by hard, brawny edema of the connective tissue about the submaxillary gland and beneath the tongue, and a raised stiff swelling of the floor of the mouth which is deep red or blue in color. The inflammatory reaction spreads in a uniform manner. The lymph nodes are not involved. The sublingual phlegmon is the dominant finding in primary Ludwig's angina. It arises primarily from the region of the submaxillary gland. Infected teeth, tonsils, breaks in the oral mucous membrane, etc., are the usual portals of entry for the bacteria. This is followed by cellulitis of the submaxillary region and then the formation of the sublingual phlegmon.

In secondary Ludwig's angina, infection of lymph nodes (mental, submental, or anterior submaxillary) or cellulitis in these areas are the foci from which the subcutaneous tissues are involved. The mode of spread to the floor of the mouth is the main point of differentiation between the primary and secondary types of the disease. In secondary Ludwig's angina, the path is directly through the muscles or their median raphe instead of through the loose areolar tissues about the posterior edge of the mylohyoid muscle, as is the case in the primary form. Cervical involvement is anterior to the submaxillary gland until very late in the disease. Because this method of spread constitutes a greater barrier to per-

foration and extension inward than does the loose cellular tissue about the submaxillary gland, the sublingual phlegmon appears considerably later in secondary than in primary Ludwig's angina. *Suppuration with pus formation in the* sublingual area does not occur until late in the course of the disease and usually is due to burrowing through of the original abscess in the lymph nodes. Until rather late in the course of the disease there is no actual pus in the sublingual tissues, and, when present, it usually represents a direct burrowing through the original abscess. The sublingual phlegmon is always secondary to lymphadenitis, cellulitis, compound fracture or osteomyelitis of the jaw, or laceration of the oral mucous membrane.

The entire course of primary Ludwig's angina is that of a rapidly spreading, fulminating cellulitis. It starts with discomfort from a carious tooth or a transitory tonsillitis which *is rapidly obscured by the pain resulting from distension* of the submaxillary region. Tension on the cervical tissues is usually great enough to force an extension to the sublingual space and the formation of the sublingual phlegmon which invades the larynx in 3 to 4 days. Fever is of high degree, and leucocytosis with a marked preponderance of neutrophiles is the rule. Death occurs usually in 9 to 12 days in untreated cases; it may be sudden in individuals who have had no evidence of respiratory distress. The manifestations of secondary Ludwig's angina are less severe and fulminating. *A history of cervical, submental, or intra-oral sepsis for* 7 to 10 days prior to the onset of the disease is common. Laryngeal involvement is much less frequent and, when present, appears much later than in the primary type.

Streptococci, predominantly of the hemolytic group, are the causative agents in about 75 per cent of the cases of Ludwig's angina. In some instances, *Staph. aureus* or pneumococci are responsible; in a few patients, 2 or all 3 of these organisms are present. Among other bacteria which have been demonstrated are *Clostridium welchii,* anaerobic strep-

tococci, spirochetes, and fusiform bacilli. Conditions which predispose to this disease are lesions of the lower lip, calculi in the submaxillary glands or ducts, and infections of the floor of the mouth, tonsils, pharynx, gums, or lower teeth, especially following extraction.

The diagnosis of Ludwig's angina is based on the clinical findings. There is usually *unilateral or bilateral massive*, brawny, tender, but rarely fluctuant swelling in the suprahyoid region, which is maximal in the submaxillary area. The overlying skin is edematous but not inflamed. The floor of the mouth is raised, swollen and hard. The mucous membrane beneath the tongue is often ulcerated and dirty-grayish white. The tongue is enlarged, and may be pushed so far upward by the sublingual edema that it fills the mouth and pharynx. It is forced downward as well, its tip protruding *between the teeth anteriorly. Pain and difficulty in opening* the mouth, in speaking, and in swallowing are the outstanding symptoms. Some degree of respiratory embarrassment is almost always present. The temperature, pulse, and respiration vary, but are usually elevated, and there is, as a rule, a moderate to high degree of leucocytosis.

All of the complications of Ludwig's angina are serious. Respiratory obstruction follows blockage of the airway by the elevated, edematous tongue, or laryngeal edema. Bronchopneumonia occurs in about 25 per cent of untreated cases. Extension of the infection takes place to the hyoid bone, the lower neck, or along the carotid sheath into the mediastinum, where abscess formation takes place. The submental and para-pharyngeal spaces may also be involved. Bacteremia is not very common Widespread suppurative gangrene of the tissues below the deep cervical fascia may also occur.

The purposes of treatment in Ludwig's angina are to establish an adequate airway, relieve tension, secure drainage, and combat infection by the use of antibiotic agents. All patients with this disease should be hospitalized. If there is

respiratory obstruction, tracheotomy should be carried out promptly. Antibiotic agents must be given as soon as the diagnosis is suspected. Since many infections are due to hemolytic streptococci, the drug of first choice is aqueous penicillin; this should be given intramuscularly in doses of 250,000 to 500,000 units every 4 hours for a minimum of 2 weeks. Other antibacterial drugs may be required, depending on the nature of the offending organism. In most cases of severe Ludwig's angina, it is necessary to drain the space under the mouth; this is done by an external incision. The exudate should be cultured and the isolated bacteria tested immediately for sensitivity to various antibiotic agents so that the most effective drug can be selected. The manipulation incident to drainage of the infected area may produce sudden, severe laryngospasm which may terminate fatally. For this reason, it has been suggested that tracheotomy be carried out prophylactically.

The prognosis in Ludwig's angina is grave. It is very important to suspect the disease early and to establish drainage and effective chemotherapy as soon as possible, keeping in mind the constant danger of respiratory obstruction. With early diagnosis, proper surgical management, preservation of a patent airway, and the administration of large quantities of potent antibiotic agents for an adequate period of time, the outlook for recovery is remarkably improved.

Infections of the Salivary Glands

Mumps (Epidemic Parotitis)

Mumps is a very common disease with affects about 80 per cent of individuals before the age of 15 years. It is worldwide in distribution, occurs most frequently in the late fall, winter, or early spring, and is more common in males than females. Cyclic epidemics appear about every 7 to 8 years.

Epidemic parotitis is due to a virus which agglutinates chicken erythrocytes, grows well in the embryonated hen's

egg, and produces typical disease after inoculation into the parotid gland of monkeys or man. It is transmitted via the respiratory tract. Active or latent cases are the reservoir for dissemination; one-third of the infections are thought to be latent. Viremia is present. The causative agent can be isolated from the blood, cerebrospinal fluid, saliva, testicle, and sydrocele fluid. The incubation period is 18 to 21 days.

The disease is communicable for from 6 days prior to the onset of glandular swelling to as long as the sixth to ninth day of clinical manifestations.

The prodromal manifestations of the mumps are variable. Some individuals are totally unaware of the infection until swelling of the salivary glands appears. In others, the parotitis is preceded by 2 to 3 days of low grade fever, generalized malaise, sore throat, and occasionally epistaxis. The temperature varies considerably; it may be low throughout the entire disease, or as high as 103-104° at the time of parotid involvement. When organs other than the parotids are affected, the meninges or testicles for example, fever to 105-106° and shaking chills may be present.

In the classic case of mumps, the parotid glands are swollen; although bilateral involvement is more frequent, unilateral disease is common. The first manifestation of parotitis may be pain behind the ear or in the auditory canal. This results from inflammation of the posterior projection of the parotid gland which is situated behind the ear lobe. In addition to the facial swelling associated with the gland itself, there is usually some edema of the tissues which surround it. The skin over the involved parotid may be reddened and tender in a rare instance. Examination of the Stensen's duct opening usually reveals swelling, enlargement of the papilla, and hemorrhage around the ductal opening. Pendulous papillae and reddening around the duct opening are frequently present in normal individuals, however. The submandibular salivary glands may be involved alone or together with the parotids; when these glands are affected,

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be affected during the course of epidemic parotitis are the lachrymal glands, thymus, breasts and pancreas. Mumps pancreatitis is probably common and is characterized by abdominal pain, tenderness under both costal margins and in the epigastrium, nausea, and vomiting. It is not hemorrhagic, does not produce necrosis of the peritoneum, is completely benign, and is not followed by fibrosis, lithiasis, or diabetes mellitus. Although difficult to detect, involvement of the ovary is said to occur in about 5 per cent of female patients. Acute prostatitis, with a varying degree of obstruction to urinary flow, appears in about 5 per cent of males. Acute mastitis is present rarely in both men and women. A most distressing manifestation of mumps is eighth nerve damage; this is usually bilateral and results in complete and irreversible deafness. It has been suggested that 3 to 5 per cent of all deaf mutism in the United States is the result of epidemic parotitis.

Orchitis occurs in about 20 per cent of men with mumps; its incidence before puberty is about 0.01 per cent. Acute epididymitis may occur alone, but usually precedes and accompanies testicular involvement. In one series of cases of orchitis, the right side was affected in 35 per cent, the left in 31 per cent, and in 33 per cent the disease was bilateral. The early stage of epididymitis is characterized by enlargement and tenderness of this organ. Severe pain, enlargement of the testicle to 3 to 4 times normal size, marked tenderness, hydrocele, and reddening and edema of the scrotal skin are the outstanding features of mumps orchitis, with bilateral disease the scrotum and its contents may approximate the size of a small grapefruit Discomfort in the lower abdomen is common. Sterility may follow mumps orchitis. A study of this problem in one group of cases revealed testicular atrophy in 35 per cent; in 90 per cent of these only unilateral involvement was present, while both testes were atrophied in 10 per cent. Although it is generally stated that mumps

they are easily palpable and tender. Swelling of the submandibular area and neck and pitting presternal edema are common with infection of these glands. Edema of the larynx with obstruction of the airway occurs rarely in submandibular mumps. The *sublingual salivary* glands may also be infected. This appears most often together with parotitis or submandibular gland involvement and is evidenced mainly by enlargement and hemorrhage around the sublingual duct openings, which are situated anteriorly on each side of the frenum of the tongue. In many cases of mumps, particularly those in which there is extensive involvement of all the salivary glands, there may be a marked suppression in secretion of saliva resulting in extreme dryness of the mouth. The so-called "acid test" which consists of pain in the parotid glands following looking at or chewing any sour food is frequently not positive, however, because complete obstruction to salivary flow is not present. Severe parotitis is usually accompanied by an increase in the serum amylase.

Mumps virus may produce disease in a number of organs other than the salivary glands; in some cases, *all* of the manifestations are extra-salivary. Thus, while meningeal reaction occurs in about 50 per cent of patients with salivary gland involvement, it appears not uncommonly as an isolated finding, and is difficult to distinguish from other types of "aseptic" meningitis (Chapter XIII). Signs of meningeal irritation, an increased number of cells, predominantly neutrophiles early and lymphocytes later, a slight to moderate increase in protein, and a normal sugar content are the characteristic findings. Mumps meningitis is always benign and leaves no residua. True meningoencephalitis is a very rare complication of mumps, and probably has the same etiology as other post-infectious encephalitides (Chapter XIII). Very rarely uni- or bilateral thyroiditis may be due to the mumps virus; this may occur in the absence of any involvement of the salivary glands. Other organs which may

glands and since the mumps virus may involve other organs and spare the salivary glands, it becomes important, in some instances, to prove the presence of the disease by means of serological study. The best method of accomplishing this is by determining the ability of the patient's serum to inhibit the agglutination of erythrocytes; this is the agglutinin-inhibition titration. Serum obtained in the acute phase of the infection is compared with that drawn 10 to 12 days later. A rise in antibody to a titer of 1:64 or higher is diagnostic. If it is necessary to ascertain whether or not a person has had mumps infection in the past, a skin test with virus antigen may be carried out. The injection of 0.1 ml. of the antigen endermally produces after 48 hours a tuberculin reaction; false positive results occur in about 10 per cent of individuals.

There is no specific treatment for mumps. None of the presently available antibodies are of any value. Although stilbesterol has been employed for the prevention and therapy of orchitis, it does not appear at present to be effective. The liberal use of analgesic agents such as codeine or demerol is indicated when pain in the face or testicles is present. The best treatment for testicular involvement is protection against trauma by surrounding the scrotum with ample quantities of absorbent cotton. Hot or cold applications or the "Bellevue bridge" are of little or no benefit. The severe headache of mumps meningitis is often promptly relieved by spinal puncture When pancreatitis occurs, intravenous hydration should be carried out until nausea and vomiting disappear. Incision of the tunica albuginea of the testicle has been recommended in instances of severe orchitis to relieve the pain, reduce the temperature, eliminate the shaking chills, and decrease the risk of testicular atrophy due to pressure. This operation should not be performed in all cases. It should be reserved for those in which pain and tenderness are very severe, and the involved testicle has an unyielding, stony hard consistency.

orchitis is of little consequence in the problem of male sterility, about 10 per cent of individuals who have had this disease have impaired fertility.

Among the less common manifestations of mumps are splenomegaly, myocarditis, involvement of the vulvovaginal glands, and rashes. The spleen may be enlarged in 20 per cent of cases. About 15 per cent of patients with epidemic parotitis have been found to have abnormal electrocardiograms; the changes appear between the fifth and tenth day of illness and last for from 4 to 35 days. Diphasic T waves, prolonged conduction time, inversion of QRS complexes, elevation of the ST segment, T wave inversion, and complete auriculo-ventricular dissociation have been observed. Precordial pain with or without palpitation may be present. Complete heart block with angina pectoris persisting for 8 and 77 days respectively has been described in 2 cases of mumps. Polyneuritis, transient facial nerve paralysis, paresis of the fifth nerve, temporary or permanent damage of the optic nerve, and transverse myelitis have been noted. Erythema nodosum, urticaria, scarlatiniform, morbilliform or vesicular rashes may appear during the course of the disease. Acute arthritis involving mainly the larger joints is observed rarely.

The white blood count in mumps is usually normal; with involvement of the testicles or meningitis, it may be increased to levels higher than 10,000. Serum amylase is often elevated when mumps pancreatitis is present, but this finding is not diagnostic of involvement of the pancreas because it is also detectable when there is severe parotitis. An increase in serum lipase above normal values indicates the presence of pancreatitis.

The presumptive diagnosis of mumps is based on clinical findings; it is confirmed by serologic studies. A history of contact with a known case, fever, and parotitis or involvement of other salivary glands or organs are highly suggestive. Since there are other causes for swelling of the parotid

lateral and occurs most often in elderly individuals with poor oral hygiene and dehydration. Suppurative parotitis used to be a relatively common postoperative complication. It may also be secondary to obstruction by a stone in Stensen's duct; in such cases, it is unilateral. Pain, facial swelling, redness and edema of the skin overlying the involved gland, and fever are always present. Milking the parotid duct yields purulent exudate containing large numbers of neutrophiles and bacteria. Shaking chills may occur. The white blood count is often elevated to high levels. Spontaneous perforation and drainage of the abscess occasionally takes place.

Suppurative parotitis is easily differentiated from epidemic parotitis on the basis of a negative history of mumps contact, the clinical findings described above, and the isolation of *Staph aureus* from the exudate obtained from Stensen's duct. Therapy must be initiated early and directed against the staphylococcus. The administration of 250,000 to 500,000 units of aqueous penicillin intramuscularly every 4 hours is recommended until the organisms have been tested for sensitivity to various antibiotics. If resistant to penicillin, the drug to which they are susceptible must be given in large quantities. Treatment is best continued for a minimum of 2 weeks. In some cases, it is advisable to incise and drain the infected parotid gland, making certain that all loculated areas of suppuration are emptied. Recovery does not take place, in some instances, unless surgical drainage is established.

Systemic Infections in Which Parotid Enlargement May Appear

Bilateral enlargement of the parotid gland may occur during the course of typhoid fever or sarcoidosis. There is usually an associated uveitis constituting the syndrome of uveo-parotid fever (Heerford's syndrome). Enlargement of

Epidemic parotitis is difficult to prevent. The best prophylaxis for mumps orchitis is to expose youngsters to the infection before puberty, when testicular involvement is rare. Immune (not normal) gamma globulin or convalescent serum, although not effective in 100 per cent of cases, may reduce very markedly the risk of development of mumps if given shortly after exposure. The administration of convalescent gamma globulin was found to decrease the incidence of orchitis, after the appearance of parotitis, from 27 per cent in control patients to 7 per cent in treated ones in a study in the Armed Forces. A formalin inactivated egg-grown mumps virus vaccine is available for active immunization. It must be administered as soon as possible after exposure; a second dose is given about one week later. Protection lasts for less than one year. Opinion concerning the effectiveness of this agent is divided. It may be of value in persons who have been exposed and have a negative skin test indicating lack of immunity. It must be pointed out, however, that this protection is only temporary and the patient may get the disease later after an exposure of which he is not aware. Mumps vaccination may have its greatest field of application in the protection of large groups of exposed persons.

Infectious and Non-Infectious Causes of Parotid Enlargement Which May Be Confused with Mumps

Not every patient with swelling of the parotid glands has mumps. There are a number of situations, both infectious and not infectious in nature, which may produce enlargement of this organ.

Suppurative Parotitis: Suppurative parotitis is due to bacterial invasion, the commonest responsible organism being *Staph. aureus.* Infection takes place by direct ascent of bacteria up the parotid duct. It is practically always bi-

CHAPTER V

INFECTIONS OF THE EARS, NOSE, PARANASAL SINUSES, AND EYES

Infections of the Middle Ear

Acute Otitis Media

Acute otitis media may occur as a primary process or as a complication of infection of the upper respiratory tract. The responsible organisms are most often the beta-hemolytic streptococcus, *Staph. aureus,* the pneumococcus, and, in children, *Hemophilus influenzae;* the latter is uncommon in adults. Regardless of the agent involved, the clinical manifestations of actue middle ear suppuration are, with rare exception, similar. Two main groups of signs and symptoms are present. The first is characteristic of infection in general and consists of fever, generalized malaise, and leucocytosis. The second results from the location of the disease and is comprised of pain which may be very intense, reddening of the tympanic membrane, a varying degree of bulging, obliteration of the light reflex and bony landmarks of the drum, and, when rupture has occurred, purulent exudate, which may pulsate synchronously with the heart beat in the external auditory canal In mild cases, the changes may be difficult to distinguish from those observed with catarrhal otitis media, especially when serous fluid is present in the middle ear. Rupture of the tympanic membrane occurs earlier with hemolytic streptococcal infection than when

the parotids has also been noted in infectious mononucleosis, trichinosis, suppuration of the lymph nodes within the glands, and *post-measles encephalitis.*

Non-Infectious Causes of Parotid Enlargement

Stone in the parotid duct is a common cause of unilateral parotid swelling. It usually produces pain, swelling and tenderness; fever and leucocytosis are absent. No saliva can be expressed from the duct on the involved side. The diagnosis is usually made by a properly carried out roentgenographic study or probing of the duct. Treatment consists of removal of the stone. Mixed tumors of the parotid gland may be responsible for unilateral enlargement of this organ and are detected by biopsy. The parotids may increase in size as a result of lymphomatous infiltration. The ingestion of large amounts of iodide or iodine may produce bilateral parotid swelling because this substance is excreted mainly through the salivary glands in which it provokes chemical irritation. Elderly individuals with chronic malnutrition, especially if the diet is inadequate in the vitamin B complex, may develop bilateral parotid enlargement. There is no fever, pain or leucocytosis, and the duration of involvement is much longer than is observed in epidemic parotitis. The administration of an adequate diet usually causes rapid return of the glands to normal size. Patients with cirrhosis and decompensation of the liver may exhibit swelling of both parotid glands which regresses with improvement in hepatic function following treatment.

may fail to respond to penicillin because the invading strain may be resistant to this agent. In such cases, it is imperative that the organism be obtained for sensitivity testing. If this cannot be done, 250 mg. of chloramphenicol plus 250 mg. of erythromycin given orally every 6 hours may prove very effective.

A difficult problem in the management of acute purulent otitis media is the question of the necessity for paracentesis. Opinion is divided as to whether surgical drainage should be instituted early in every case, or whether it should always be avoided. Those who favor early paracentesis most strongly insist that antibiotic therapy, while eradicating the organisms, does not eliminate the possibility of organization of the exudate in the middle ear which may result in the eventual development of loss of hearing. The writer does not recommend surgical intervention unless the following conditions are present: (1) Pain in the ear is increasing and becoming unbearable and difficult to control with drugs. (2) The infection in the middle ear is failing to respond to treatment, and it becomes necessary to obtain exudate for bacteriologic studies (3) There is evidence of rapidly progressing deafness. (4) Early mastoiditis with destruction of bone is present. To perform *paracentesis in every patient is* as unwise as it is to refuse to carry out this procedure in every case. Each situation must be studied carefully, and the decision made on the basis of the findings and the course of the disease.

Chronic Otitis Media

The bacteriologic and clinical findings in chronic otitis media are different from those of the acute type of infection. Persistence of disease in the middle ear for a long period is characterized by simultaneous slow destruction and overgrowth of tissues. Pain is infrequent or minimal except when exacerbation occurs. The outstanding signs are the presence of foul smelling exudate in the external auditory canal and

other organisms are involved; it may take place in less than 24 hours after onset of the disease. When other bacteria are responsible, *Staph. aureus*, the pneumococcus, or *H. influenzae* for example, spontaneous perforation of the tympanic membrane may require 3 to 4 days or longer, or may not occur at all.

The diagnosis of acute suppurative otitis media is based on detection of the characteristic changes in the ear and the presence of fever and other manifestations of infection. The problem of greatest importance is determination of the type of organism producing the disease. If the drum has ruptured, gram stain of the purulent exudate in the external canal is very helpful in revealing the causative bacteria. When the tympanic membrane is still intact, the etiology is suspected usually on a statistical basis. Thus, the pneumococcus, *Staph. aureus*, and the beta-hemolytic streptococcus are commonest in adults, and *H. influenzae* is most frequent in children. Early rupture of the tympanic membrane suggests the possibility of beta-hemolytic streptococcal infection. Exudate must always be cultured on appropriate media in order that the responsible organism may be identified and be available for testing of sensitivity to various antimicrobial drugs.

The treatment of acute purulent otitis media with antibiotic agents is usually very successful. In adults, the drug of choice is penicillin. The usual therapy consists of the administration of 600,000 to 1,000,000 units of procaine salt once daily, or 250,000 units of aqueous benzyl penicillin G intramuscularly every 6 hours. Oral treatment may be effective in mild cases, if started early; it cannot be recommended for routine use, however. Therapy should be continued for about 10 days. In children, because of the frequency of *H. influenzae* infection, it is best to give tetracycline or chloramphenicol in a dose of 50 to 75 mg. per Kg. of body weight divided into equal quantities which are administered 4 times a day. Otitis media due to *Staph. aureus*

and intensive chemotherapy of the middle ear disease, involvement of the mastoid bone may be prevented in many instances. The bacteria responsible for acute mastoiditis are the same as those most frequently present in acute otitis media; they may be different, however. Occasionally, for example, the *beta-hemolytic streptococcus is isolated from* the exudate in the external auditory canal, while *Staph. aureus* is recovered from the mastoid at operation. The signs and symptoms of acute mastoiditis are (1) bulging of the posterior wall of the auditory canal, (2) an increase in the quantity of the pulsating discharge, and (3) tenderness, redness, pain and swelling over the mastoid bone, the appearance of marked fluctuation indicates the development of a subperiosteal abscess. High grade fever and leucocytosis with a preponderance of neutrophiles are observed in practically all cases. X-ray study of the mastoid bone, in the early stages, reveals fluid in the air cellules; later the septa show a varying degree of destruction.

The treatment of choice in early mastoiditis is penicillin. The crystalline benzyl G compound (aqueous) is administered in an intramuscular dose of 250,000 to 500,000 units every 6 hours. Procaine penicillin may not be effective, because it tends to produce blood levels which may be too low to eradicate the organisms from the infected bone. In cases in which penicillin-resistant strains of *Staph. aureus* are involved, it is necessary to test for sensitivity to other antibiotics, mainly chloramphenicol, erythromycin, tetracycline, and bacitracin, the agent producing the maximal degree of suppression of bacterial growth *in vitro* should be given in adequate quantities. Treatment should be continued for no less than 2 weeks. In young children, because of the frequency with which *H. influenzae* is implicated, initial therapy with either tetracycline or chloramphenicol (50 to 75 mg per Kg. per day, divided into 4 equally spaced doses) is indicated. When chemotherapy for mastoiditis is started late in the course of the disease, it is frequently not

decreased auditory acuity. The tympanic membrane is the site of a perforation of varying size or may be completely absent. Granulation tissue is present, and cholesteatoma formation is frequent. X-ray examination of the mastoid on the involved side usually reveals some degree of bone damage with sclerosis.

The organisms isolated from cases of chronic otitis media most frequently are *E. coli, Ps. pyocyaneus, Proteus, A. aerogenes, Staph. aureus, Staph. albus,* alpha or non-hemolytic streptococci, and diphtheroids. The gram-negative bacteria and staphylococci are usually predominant. Although there may be some question of the significance of these organisms in the pathogenesis of prolonged middle ear infection in some instances, the fact that they can be isolated *with great frequency mitigates against their being simple* contaminants.

The medical treatment of chronic otitis media is most often not effective. Nevertheless, it is worthwhile, especially in cases in which surgery is contraindicated or the patient refuses operation, to try the administration of antibiotics which must always be selected only on the basis of the sensitivities of the organisms which have been isolated. The most effective agent should be given in large quantities for at least 2 weeks. Both oral or parenteral and local treatment have been applied. This kind of management may halt the disease in a small number of cases. In many, however, it produces only temporary relief and the drainage from the ear recurs. *Failure is probably related to the difficulty in* eradicating the bacteria because of the presence of cholesteatoma and granulation tissue. Radical mastoidectomy is indicated when an adequate trial of chemotherapy does not produce the desired result.

Acute Suppurative Mastoiditis

Infection of the mastoid is the commonest complication of acute purulent otitis media. With early, properly selected

terior nares and is often provoked by pulling out or cutting the nasal hairs. The organism most frequently responsible is *Staph. aureus*. The initial lesion is a small "pimple" or furuncle which is usually very painful and tender. As the infection progresses, the local area increases in size, redness and swelling of the external nose develop, the nasal mucous membrane becomes turgid and occludes the airway, and lymphangitis with obstruction occurs and produces marked inflammation and edema of the upper lip, the tissues lateral to the nose, and the periorbital areas. Fever is usually high, and shaking chills may occur in severe cases. The white blood count is elevated, often to high levels, and there is a striking increase in young neutrophiles. The major complications are bacteremia with metastatic infection of various organs and thrombophlebitis of the ophthalmic vein with extension to the cavernous sinus, which becomes infected and thrombosed.

The diagnosis of intranasal furuncle is established by physical examination. Since most cases are due to *Staph. aureus*, treatment should be directed against this organism. Cultures of the blood and nasal exudate, if present, should always be made before therapy is initiated, so that the responsible bacteria will be available for study should the treatment first applied prove ineffective. Because of the possibility of involvement of a penicillin-resistant strain and the danger to life associated with rapid progression of the disease, it is best to initiate therapy with 0.5 gm. of chloramphenicol plus 0.5 gm of erythromycin orally or intramuscularly every 6 hours. If studies of the recovered organisms indicate lack of sensitivity to these agents, the drugs to which they are most susceptible must be given in large quantities. The minimum period of treatment is 2 weeks. The presence of bacteremia or cavernous sinus involvement makes the outlook for recovery difficult to predict even when effective antibiotic agents are given. The local lesion in the nose must not be interfered with. It must *never* be

curative. In such cases, simple mastoidectomy is often necessary to eradicate the infection. The appearance of acute mastoiditis while a patient is being treated for otitis media indicates the presence of an organism insensitive to the drug being given and necessitates an immediate change to the antimicrobial agent found by bacteriologic study to be the most effective. All patients with mastoiditis must be observed very carefully for the development of the common complications of this disease; these are lateral sinus thrombophlebitis, extradural abscess, brain abscess, and purulent meningitis.

Infections of the Nose

Nasal Diphtheria

Diphtheria is occasionally restricted to the mucous membranes of the nose. The lesion is usually localized to one side and is present most often on the anterior portion of the septum or on the turbinates. Persistent, unilateral, serosanguinous discharge is characteristic. Examination reveals a bluish-white or gray membrane which leaves bleeding areas when removed and is surrounded by a narrow zone of inflammatory reaction. When the disease involves the posterior portion of the nose, extension to the pharynx may take place. The membrane usually persists for a long time without the appearance of toxic manifestations.

The diagnosis and treatment of nasal diphtheria are the same as for faucial infection by the same organism and are described in Chapter VI. The dose of antitoxin when the nose alone is involved is 5,000 to 10,000 units. The presence of foreign body or any other cause of chronic nasal obstruction must be ruled out because this favors the development and persistence of the disease.

Intranasal Abscess

Intranasal furuncle is one of the most dangerous infections. It usually starts in one of the hair follicles in the an-

or disease of all may be present simultaneously—pansinusitis.

Fever and leucocytosis are very common, and chills may occur occasionally in acute sinusitis. The clinical manifestations vary, depending on the specific sinus affected. Headache, pain, tenderness, and, in severe cases, redness, heat, and swelling of the skin of the lower forehead are the findings in frontal sinusitis. A purulent discharge is present in the middle meatus of the nasal turbinates. When the frontal bone becomes involved and osteomyelitis develops, the characteristic sign is pale, cool, doughy edema of the skin over the frontal sinuses. Maxillary sinusitis is characterized by swelling and tenderness over the maxilla, and pain not infrequently referred to the teeth. In severe infections, the hard palate is swollen, the upper teeth are loosened, and there may be hemorrhage in the surrounding tissues. Purulent exudate is detectable in the middle meatus. Infection of the ethmoid sinuses is accompanied by reddening and tenderness over the upper lateral aspects of the nose. Sterile orbital inflammatory reactions may occur and produce conjunctivitis and protrusion and chemosis of the eyeball. In some instances, perforation of the lamina papyracea takes place and orbital cellulitis or abscess develops. The ocular proptosis in this type of disease can be differentiated from that observed in cases of cavernous sinus thrombosis, because in the latter, total ophthalmaplegia is the rule. The appearance of epistaxis suggests thrombosis of the ethmoidal veins. Purulent exudate is found in the middle (anterior ethmoid cells) or superior nasal meatus (posterior ethmoid cells). In sphenoid sinusitis, pain is usually present over the occiput, and tenderness may be detected over one or both mastoid bones. Pus is present in the superior meatus. Involvement of this sinus may produce no clinical manifestations.

The complications of paranasal sinusitis are frontal bone

squeezed. Surgical drainage should not be carried out unless the abscess is large and very painful. The incision should be limited to the fluctuant, necrotic area. The application of moist heat to the nose is often very helpful. Analgesic agents such as codeine or Demerol may be used freely when pain is severe.

Nasal Syphilis

Acute rhinitis is a feature of active syphilis in the newborn child. The outstanding manifestation is a mucoid or bloody nasal discharge. This syndrome has often been referred to as the "snuffles". The diagnosis of syphilitic rhinitis is confirmed by demonstration of *Treponema pallida* in dark field preparations of the nasal discharge, but it may be suspected when other physical stigmata of the disease are detectable in the child or the serologic test is positive in the mother. A positive reaction in the baby's blood does not establish the presence of the infection since it may be due to passive transfer of antibody from the mother. Serial titrations must be carried out. If the level of reagin falls rapidly, syphilis is not present; if it remains stationary or rises, antiluetic treatment must be instituted. The therapy of lues is discussed in Chapter XII. The nasal septum may be involved in acquired syphilis with the formation of a gumma and eventual perforation.

Infections of the Paranasal Sinuses

Acute Sinusitis

Bacterial invasion of the paranasal sinuses is usually secondary to upper respiratory infection and is due to the same types of organisms which are most often responsible for pharyngitis or acute otitis media, namely *Staph. aureus*, the beta-hemolytic *Streptococcus*, the *pneumococcus*, and *H. influenzae*. Any one of the sinuses may be infected alone

such as *Ps. pyocyaneus* and *Proteus*, are detectable in the chronic type. The clinical manifestations are non-specific. Headache which usually appears in the afternoon or shortly after rising in the morning, post-nasal discharge, a varying degree of tenderness over the involved sinuses, and nasal obstruction are common. Purulent exudate may be present in the middle or superior meatus of the nasal turbinates. Transillumination may reveal "clouding" and x-ray study demonstrates thickening of the mucous membranes, with or without fluid, in the affected sinuses. The symptoms of chronic sinusitis may be present in unrelated, non-infectious conditions. Allergic or vasomotor rhinitis is an example. It has been said that not a small number of patients who have been treated for "chronic sinusitis" for long periods of time are really suffering from a psychoneurosis.

If true chronic sinusitis is present, a trial of antibiotic therapy selected on the basis of sensitivity of the organisms to specific drugs may be worthwhile. The simultaneous application of vasoconstricting agents to the nasal mucous membrane may help establish adequate drainage. Many patients fail to do well with any type of "medical" treatment and should be referred to the otolaryngologist.

Infections of the Eye

Gonococcal Ophthalmia

Inoculation of the conjunctival sac of babies with *N. gonorrheae* usually occurs during birth. The incubation period is 2 to 3 days; the relatively short period elapsing between exposure and the appearance of manifestations helps to distinguish this infection from inclusion blenorrhea which also occurs in the neonatal period. The first signs of gonococcal conjunctivitis are marked hyperemia, edema of the eyelids, and purulent discharge. If a diagnosis is made early and therapy instituted, cure is rapid and corneal involvement does not take place. If, however, the disease is not

osteomyelitis, cerebral venous sinus thrombosis, brain abscess, orbital cellulitis or abscess, extradural abscess, meningitis, and bacteremia with metastatic infection of various organs.

The diagnosis of acute purulent sinusitis is usually made on the basis of the clinical findings described above; transillumination studies and roentgenograms reveal the presence of fluid and thickening of the mucous membranes. The etiology of the disease is determined by culture of the nasal discharge or of exudate obtained by surgical drainage.

The therapy of choice in acute sinusitis is one of the antibiotic agents. When the disease is very severe and delay in treatment does not appear wise, the injection of crystalline benzyl penicillin G, 250,000 units intramuscularly every 4 hours, is indicated *after cultures have been obtained.* In children, tetracycline (75 to 100 mg. per Kg. per day divided into 4 equally-spaced doses) may be more effective than penicillin because of the frequency with which *H. influenzae* is the causative agent. All strains of *Staph. aureus* isolated from the sinuses must be examined for sensitivity to various antimicrobial agents, and the one to which they are most susceptible administered in adequate quantities. Regardless of the drug used, treatment should be continued for about 2 weeks. Establishment of free drainage by means of nasal packs wet with a vasoconstricting agent like neosynephrine is often very helpful. In cases which respond slowly to therapy, it may be necessary to establish surgical drainage of the involved sinus, in addition to giving chemotherapy, before cure is accomplished.

Chronic Sinusitis

The diagnosis of chronic sinusitis is undoubtedly made much more frequently than the disease is actually present. There is no question, however, that infections of the sinuses may become chronic. The same organisms which are present in the acute form, in addition to gram-negative bacteria

such as *Ps. pyocyaneus* and *Proteus*, are detectable in the chronic type. The clinical manifestations are non-specific. Headache which usually appears in the afternoon or shortly after rising in the morning, post-nasal discharge, a varying degree of tenderness over the involved sinuses, and nasal obstruction are common. Purulent exudate may be present in the middle or superior meatus of the nasal turbinates. Transillumination may reveal "clouding" and x-ray study demonstrates thickening of the mucous membranes, with or without fluid, in the affected sinuses. The symptoms of chronic sinusitis may be present in unrelated, non-infectious conditions. Allergic or vasomotor rhinitis is an example. It has been said that not a small number of patients who have been treated for "chronic sinusitis" for long periods of time are really suffering from a psychoneurosis.

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recognized and allowed to progress, keratitis with ulcer formation develops. Penetration of the cornea follows. Scarring results, and, because the disease is bilateral, total blindness is the end result.

The presence of gonorrhea in the mother should make the physician aware of the possibility of its transmission to the eyes of the child. The specific diagnosis of the disease is easily established by the demonstration of gram-negative, intracellularly-situated, biscuit-shaped diplococci in the conjunctival exudate. Cultural and biochemical studies must be carried out in every case, however, in order to establish the exact identity of the organism and to distinguish it from non-pathogenic *Neisseria* and the meningococcus. The oxidase test is positive with *N. gonorrheae,* and it ferments only glucose. Treatment must not be delayed until precise identification of the bacteria has been accomplished; the presence of an acute purulent conjunctivitis in which typical gram-negative diplococci are present necessitates the immediate administration of chemotherapy.

Penicillin is the agent of choice for the treatment of gonococcal conjunctivitis. The injection of 600,000 units of the procaine ester of this agent once daily for 5 to 6 days produces rapid cure. Aureomycin and erythromycin may also be effective, but penicillin is preferred. It is not necessary to apply the antibiotic to the conjunctival sac.

Gonococcal ophthalmia is a preventable disease. Detection of gonorrhea in the mother and its eradication before parturition is the most effective method of protecting the child against infection. The instillation of silver nitrate solution into the conjunctival sac of all infants at the time of birth is compulsory and very effective. If this agent is not properly washed out after a proper interval, however, it may produce a chemical conjunctivitis which may be easily confused with an infectious process. The application of penicillin solution to the eyes of newborn infants has

been shown to protect against gonococcal invasion, and the drug is not irritating. This procedure cannot be adopted as standard practice, however, because of laws in many areas which make the use of silver nitrate mandatory.

Conjunctivitis due to Various Species of Hemophilus ("Pink Eye")

Three members of the *Hemophilus* group of bacteria may cause acute purulent conjunctivitis. An epidemic form which occurs most commonly in the summer is due to the Koch-Weeks bacillus (*H. egyptius*). The Morax-Axenfeld bacillus (*H. duplex*) is also responsible for epidemic conjunctivitis and has been incriminated in outbreaks associated with swimming pools. The third species which may be involved is *H. influenzae;* disease produced by this organism is usually sporadic, occurs most often in the winter, and is not infrequently secondary to respiratory tract infection by this agent. Although it was thought at one time that the Koch-Weeks bacillus and *H. influenzae* were the same organism, they have been shown to be distinct species, the former agglutinates red blood cells while the latter does not. The signs and symptoms of acute bacterial conjunctivitis are ocular discomfort, photophobia, reddening and swelling of the conjunctiva, and purulent exudate. These are the same, regardless of the type of organism involved. The etiology of the infection can be determined, therefore, only by bacteriologic study. Gram-stained smears and cultures of the conjunctival exudate must be carried out in every case. Blood and "chocolate" agar should be used. The therapy for the conjunctival infection produced by any of the types of *Hemophilus* consists of the instillation of tetracycline or chlortetracycline (Aureomycin) ointment, or an aqueous solution of sulfacetamide into the conjunctival sac 2 to 3 times a day for one week. Cure following this type of treatment is usually rapid, and complications or recurrences do not develop.

Conjunctivitis and Ophthalmitis due to Other Bacteria

Staph. aureus, the pneumococcus, beta-hemolytic streptococcus, meningococcus, *Ps. pyocyaneus*, and other bacteria may cause disease of the eye. This may appear as a complication of respiratory tract infection due to these organisms, or as isolated disease, especially when *Ps. pyocyaneus* is the inciting agent. The signs and symptoms are the same as those produced by invasion by the gonococcus or *Hemophilus*. Corneal ulceration and perforation, vitreous abscess, and involvement of the entire eye resulting in loss of vision are common in the absence of therapy. The use of fluorescein contaminated with *Ps. pyocyaneus* for the visualization of corneal injuries has led to the development of a severe ophthalmitis. *Pseudomonas* is very actively proteolytic and perforation of the cornea and infection of the whole eye follow its inoculation with great rapidity. The diphtheria bacillus may rarely produce conjunctivitis; the formation of a membrane in the conjunctival sac identical to that present in the pharynx with faucial diphtheria is characteristic

The etiologic diagnosis of the various types of bacterial disease of the eye is made on the basis of gram-stained smears and cultures. The choice of chemotherapy depends on the causative organism. For staphylococcal infection, instillation of solutions of bacitracin or penicillin (200,000 units per ml.) into the conjunctival sac several times a day is effective in most instances; when the eye itself is involved, it is best to give 250,000 units of penicillin G (crystalline benzyl) intramuscularly every 6 hours, or 0.5 gm. of chloramphenicol plus 0.5 gm. of erythromycin orally 4 times a day. Therapy should be continued for 7 to 10 days. When *Pseudomonas* is involved, the drug for local use is polymyxin. Oral administration of sulfadiazine or sulfisoxazole (Gantrisin) is effective in the management of meningococ-

cal conjunctivitis or ophthalmitis; the dose for adults is 4 gms. followed by one gm. every 4 hours for at least one week. Conjunctival diphtheria responds to antitoxin; an adequate dose is 10,000 to 20,000 units.

Inclusion Blenorrhea

Inclusion blenorrhea is a viral disease which affects primarily newborn children, produces purulent exudate, and may be confused with gonococcal conjunctivitis. Unlike gonorrhea which usually occurs 3 to 4 days after birth, it is rarely observed in infants younger than one week. The diagnosis of inclusion blenorrhea is based on the demonstration of typical inclusion bodies in Giemsa stains of conjunctival scrapings. The causative agent is present in the vagina of the mother from which it is inoculated into the eye of the baby during parturition. Sulfadiazine or Gantrisin, 0.1 gm. per lb. of body weight administered orally in divided doses per 24 hours, with half of the required daily quantity being given initially, produce cure.

Trachoma

Although trachoma is observed most frequently in Europe and the Near and Far East, it occurs occasionally in the United States in individuals who have migrated from endemic areas and in those who live in Missouri, Arkansas and southern Illinois. The disease is due to a virus and is highly contagious.

The onset of trachoma may be fulminating or insidious. One of the first signs is hyperplasia of the lymphoid tissue, especially of the upper lids. Later, the lids become swollen and everted, and the conjunctivae are red, edematous, and studded with innumerable red and yellow follicles. There is little or no purulent exudate in the acute phase unless secondary bacterial infection takes place. The chronic stage of trachoma appears several weeks after onset of the infection and is characterized primarily by the development of a pan-

nus consisting of fibroblasts and blood vessels. This invades the cornea, produces ulceration, and, with organization, leads to scarring and eventually to total loss of vision.

The diagnosis of trachoma is suspected when the characteristic clinical findings are present in an individual who lives in or has recently left an endemic area. Demonstration of the typical cytoplasmic inclusion bodies in stained preparations of conjunctival and corneal scrapings establishes the etiology.

There is no specific cure for trachoma. The sulfonamides are the best drugs for treatment and should be given in full doses for at least 2 weeks. Oxytetracycline (Terramycin) and chlortetracycline (Aureomycin) are active against the trachoma virus; chloramphenicol is much less effective, and penicillin, bacitracin, and streptomycin are of no value. When the chronic stage of the disease is present, therapy includes removal of pannus together with administration of a sulfonamide compound. Trachoma tends to relapse. There are no definite criteria for cure, but quiescence of inflammation, deturgescence of the pannus, resolution of the follicles, return of the color of the conjunctiva to the normal pink, and absence of inclusion bodies indicate that the process is arrested.

Herpes Simplex (Dendritic Keratitis)

Dendritic keratitis is due to invasion of the cornea by the virus of herpes simplex. The typical lesion has a branched appearance from which the disease derives its name. As a rule, involvement is unilateral. Loss of corneal sensitivity distinguishes this disease from other forms of keratitis. There is usually circumcorneal injection. Slit-lamp examination reveals the characteristically-shaped ulcer. Secondary bacterial invasion may result in perforation of the cornea and ophthalmitis. Like other syndromes due to herpes simplex, the keratitis has a tendency to recur; the greater the

number of attacks, the more severe the corneal scarring and impairment of vision.

The diagnosis of dendritic keratitis is based on the presence of pericorneal inflammation, absence of corneal hypersensitivity, and demonstration of the typical ulcer by slit-lamp examination. There is no agreement concerning the effectiveness of antibiotic therapy; it is probably of no value, although the application of Aureomycin drops or ointment to the eye has been claimed to produce cure by some investigators. Although Cortisone ointment has been employed locally, its use in the acute phase is contraindicated because of the danger of perforation of the cornea; the corticosteroid may be of help late in the disease to decrease the risk of disabling scarring. Atropine should be instilled in the conjunctival sac except in middle-aged or elderly individuals in whom such treatment may precipitate an episode of acute glaucoma. All patients with dendritic keratitis should be referred to an ophthalmologist for treatment.

Epidemic Keratoconjunctivitis

Keratoconjunctivitis is an epidemic form of eye infection which is produced by more than one kind of virus. An agent closely related to that responsible for St. Louis encephalitis and one type of adenovirus have been isolated. The disease is usually unilateral and involves primarily the eyelids, although keratitis may develop and cause corneal perforation. Secondary bacterial invasion may take place. The commonest symptom is a "sandy" feeling in the involved eye. There is conjunctival and circumcorneal inflammation. Few or no general manifestations may be present, although severe headache and high fever are notable in some cases. The pre-auricular node on the affected side is enlarged. Encephalitis is a rare complication.

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CHAPTER VI

INFECTIONS OF THE UPPER RESPIRATORY TRACT

Approximately two-thirds of all the illness that involves families affects the upper respiratory tract. Only about 3 per cent are due to agents which are affected by antimicrobial drugs, however. Children between the ages of 1 and 6 years suffer an average of eight respiratory infections per year of which only one, or at the most two, are due to bacteria. After the age of six, this type of disease decreases in frequency, but in an average family there are still about six infections of the respiratory tract in each person per year. The incidence is lowest in elderly individuals. The reason for this is not known, but it is probably not due to the development of specific immunity.

INFECTIONS OF THE PHARYNX

The symptoms and signs which develop with pharyngitis are, with a few exceptions, qualitatively similar, although quantitatively they are quite variable, some being mild and others very severe. The physical changes which appear with invasion of the pharynx by different microorganisms are, for the most part, not sufficiently characteristic to allow an etiologic diagnosis to be made. There are some exceptions to this generalization; these are discussed in detail below. As the physician gains increasing experience with the problem of pharyngeal infection, he becomes increasingly aware

epidemic of conjunctivitis occurs in which the eye involvement is primarily unilateral. It can be proved by the demonstration of a rising antibody titer to either type of virus. There is no specific treatment.

Newcastle Virus Conjunctivitis

Newcastle virus infection produces an epidemic disease of chickens characterized by pneumoencephalitis in young birds and pneumonia in older ones. Individuals who work with infected fowl may develop a conjunctivitis, especially if blood from the chickens is accidentally introduced into the conjunctival sac. The characteristic manifestation is unilateral conjunctival inflammation with or without ipsilateral preauricular lymphadenopathy. Chills may be present, although fever is uncommon. The diagnosis can be established by isolation of the virus from the conjunctival exudate; this is not practical, however. Detection of a rising titer of neutralizing antibody for Newcastle virus in serums obtained early and late in the course of the infection establishes the specific etiology. None of the presently available sulfonamides or antibiotic agents are of therapeutic value.

CHAPTER VI

INFECTIONS OF THE UPPER RESPIRATORY TRACT

Approximately two-thirds of all the illness that involves families affects the upper respiratory tract. Only about 3 per cent are due to agents which are affected by antimicrobial drugs, however. Children between the ages of 1 and 6 years suffer an average of eight respiratory infections per year of which only one, or at the most two, are due to bacteria. After the age of six, this type of disease decreases in frequency, but in an average family there are still about six infections of the respiratory tract in each person per year. The incidence is lowest in elderly individuals. The reason for this is not known, but it is probably not due to the development of specific immunity.

Infections of the Pharynx

The symptoms and signs which develop with pharyngitis are, with a few exceptions, qualitatively similar, although quantitatively they are quite variable, some being mild and others very severe. The physical changes which appear with invasion of the pharynx by different microorganisms are, for the most part, not sufficiently characteristic to allow an etiologic diagnosis to be made There are some exceptions to this generalization, these are discussed in detail below. As the physician gains increasing experience with the problem of pharyngeal infection, he becomes increasingly aware

of the difficulty involved in establishing the cause of a sore throat purely on the basis of physical examination.

Acute and chronic pharyngitis may be produced by bacteria, viruses, spirochetes, and fungi. Mechanical and psychogenic factors may cause sore throat difficult to distinguish from that due to infection.

Streptococcal Tonsillopharyngitis

The incubation period of streptococcal tonsillopharyngitis is about 48 to 72 hours; it may be as short as 18 hours or as long as 7 days. The earliest manifestations are pharyngeal discomfort, generalized malaise, and fever varying from 99° to 104°F. About one-third of patients have manifestations which are so minimal that they do not visit a physician, or if they do, the presence of streptococcal infection of the throat cannot be suspected on the basis of the physical findings. In severe cases, throat pain is marked and swallowing very difficult. The pharynx is beefy red in color and edematous, and the tonsils and other lymphoid tissues are swollen. In some instances, there is considerable exudate, this is discrete, distributed in "patches," yellow in color, most prominent in the tonsillar crypts and on the lymphoid follicles, and wipes off easily leaving no ulcers or bleeding points. There is leucocytosis with an increase in neutrophiles. When the disease is mild, there is only a varying degree of hyperemia and injection of the blood vessels, and the white blood count may be normal.

A chronic form of streptococcal infection of the pharynx occurs in children less than 3 years of age. The onset is insidious and the constitutional reaction subacute. There is frequently a mild rhinopharyngitis with a slight, thin, excoriating discharge from the nose. The fever is moderate at first; it then becomes low grade and may persist for from 4 to 8 weeks. There is usually bilateral cervical adenitis which occasionally becomes suppurative. Catarrhal or purulent otitis media may appear. The complexion is muddy.

Slight anemia and a mild degree of leucocytosis are common. Anorexia is present in almost all cases. Behavior is erratic. Convalescence may be quite prolonged. Bacteriologic study of the nose and throat reveals group A *Strep. pyogenes* in pure culture, or as the predominating organism.

Scarlet fever is a form of streptococcal tonsillopharyngitis, although the portal of entry for the organisms may be a site other than the upper respiratory tract. The only distinguishing feature is the punctate, erythematous rash. This disease is discussed in detail in Chapter XVI.

The complications of streptococcal pharyngitis are of two types; suppurative and non-suppurative. The suppurative complications result from direct spread of the organisms from the throat or from invasion of the blood stream. Peritonsillar or parapharyngeal space abscess, otitis media, mastoiditis, meningitis, laryngitis, tracheitis, or pneumonia follow extension of infection from the pharynx. Paronychia are produced by the introduction of streptococci around the nails, when the fingers are placed in the mouth. Contact of the skin of the face with nasal discharge containing the bacteria may produce impetigo. Bacteremia leads to the development of metastatic foci of infection in many organs; the organisms localize most frequently, however, in the meninges, heart valves, and synovial membranes.

The non-suppurative complications of streptococcal sore throat usually appear after a latent period and occur most frequently in from 10 days to 6 weeks after invasion by the organism has first taken place. Rheumatic fever and acute glomerulonephritis are the most common late sequelae. Rheumatic fever occurs in about 2.5 per cent of patients with streptococcal tonsillopharyngitis and is most common in children aged 5 to 10 years, although primary attacks and recurrences may develop at any age. The disease which initiates it may be very mild and not be detected by the patient or the physician. Diffuse glomerulonephritis follows deep-seated or superficial streptococcal infections such as

pharyngitis, infected eczema, erysipelas, cellulitis, or meningitis. There is usually a latent period of 2 to 6 weeks between the development of the acute infection and the appearance of laboratory and clinical evidence of renal involvement.

Fever of low degree which persists for weeks or even months may follow streptococcal pharyngitis. Rheumatic fever or the childhood type of streptococcosis must be considered in these cases; in many instances, the cause cannot be discovered and the pyrexia eventually disappears. Arthralgia involving one or more of the larger joints may appear 2 to 6 weeks after the onset of infection; the joints may be red and swollen. Although often presumed to be the rheumatic state, this cannot always be proved since no other laboratory or clinical manifestations of this disease are present.

Various types of rashes may occur in 2 to 4 weeks after the onset of streptococcal sore throat. Erythema nodosum or erythema marginatum appear occasionally, the latter is considered by some to be one of the major criteria of rheumatic fever. Purpura is rare; it may be widely distributed and loss of epidermis or part of an extremity may follow. Periarteritis nodosa is a very rare late complication. A very unusual sequel is scleredema adultorum. This is characterized by progressive induration and non-pitting edema of the deeper parts of the skin and subcutaneous tissues which become firm and rigid and cannot be lifted into folds. Atrophy, pigmentation, or signs of inflammation are absent. The changes often begin about the back of the neck and spread to involve the front of the neck, face, back, and chest. The lower extremities are less affected than the upper ones, and the hands and feet usually are spared. A transitory erythematous rash may precede the induration. The entire process usually disappears completely within one year, leaving normal skin in the previously involved areas.

The diagnosis of streptococcal pharyngitis is usually made

when edema, redness, lymphoid tissue enlargement, and exudate are present in the throat. These features are often lacking in mild cases, however. Even when they are all detectable, diagnostic difficulty may still arise because they may also be observed, in varying degree, in early diphtheria, infectious mononucleosis, or exudative viral pharyngitis. The only positive method of establishing the diagnosis of streptococcal pharyngitis is isolation and identification of the organism. This is readily done on blood agar media. Even with the best technical procedures, streptococci can be recovered in no more than 90 to 95 per cent of cases. Material obtained by throat swab should be cultured as quickly as possible and not allowed to dry. The recovery of the bacteria does not always indicate a causal connection between them and the disease process, because they may represent only a carrier state. In order to prove the etiologic relationship, it is necessary to show that the streptococcus possesses group A polysaccharide. This is only very rarely indicated, but it may be important in evaluating the clinical significance of the organism; if it is a member of groups other than A, C or G, it is probably of little or no significance.

If a diagnosis of streptococcal pharyngitis cannot be established during the acute phase, it can often be proved retrospectively by serological methods. The most valuable procedure is estimation of serum antistreptolysin titer. This antibody inhibits oxygen labile streptolysin O, first appears about 2 weeks after infection, and increases in quantity for the next 4 to 6 weeks; it may remain at elevated levels for many months and possibly even for several years Titers of 125 units or over are significant. An increase in antistreptolysin is not diagnostic of rheumatic fever; it merely indicates recent experience with the beta-hemolytic streptococcus. Anti-streptokinase appears in the serum of about 20 per cent of patients who have group A streptococcal infections. Type-specific antibacterial immunity is first detectable in

from 5 to 6 weeks after infection and may persist for a year or more; it is protective only against the serological type which provoked its production and is ineffective against all other types. Therapy with penicillin or Aureomycin depresses the formation of antistreptolysin, antistreptokinase and antibacterial antibody.

There is at present no practical method for producing type-specific antibacterial immunity against the beta-hemolytic streptococcus. Prophylaxis in the individual exposed to this organism is best carried out by giving penicillin. The administration of 200,000 units of this agent orally every 12 hours for 4 to 5 days produces protection against infection. A single injection of 600,000 units of Bicillin is also effective. One of the most important aspects of the prevention of streptococcal disease is proper therapy of the acute case. Since patients adequately treated with antibiotic are free from streptococci in a short time, the number of convalescent carriers who might disseminate the organism is markedly reduced. It is not necessary to quarantine contacts with the possible exception of food handlers who can be allowed to return to work after 4 days of chemoprophylaxis. Erythromycin, 250 mg. every 12 hours orally, should be used in individuals with known sensitivity to penicillin.

The treatment of streptococcal pharyngitis with sulfonamides is of questionable value since the effect of these agents on the course of the disease and the eradication of organisms from the pharynx is inferior to that of other antimicrobial drugs. Penicillin is the antibiotic of choice in the therapy of this infection because it not only produces rapid clinical cure and eradication of the streptococci but also prevents the appearance of suppurative complications. It has also been suggested that the incidence of rheumatic fever and glomerulonephritis is appreciably reduced. Several schedules of therapy may be employed. The administration of 300,000 or 600,000 units of procaine penicillin intramuscularly once a day is very adequate. Alternate procedures

are the intramuscular injection of 300,000 units of aqueous penicillin every 12 hours or a single parenteral dose of 1,200,000 units of benzethacil (Bicillin). Oral treatment is also very effective; 200,000 units of buffered penicillin G or the same quantity of penicillin V given every 8 hours produces rapid cure. Erythromycin, 250 mg. orally every 6 hours, can be substituted in penicillin sensitive patients. Treatment must be continued for 10 days. The "broad-spectrum" antibiotics should not be used because they do not eradicate the organisms, and relapse of pharyngitis may occur after therapy has been stopped. The rapid healing of streptococcal pharyngitis by penicillin does not eliminate the necessity of careful clinical follow-up study for the next 4 to 6 weeks in order to detect the development of rheumatic fever, glomerulonephritis, or other complications.

Diphtheria

Diphtheria is acquired by contact with active cases or asymptomatic carriers. Although most children are immune to the disease, a recent study in Massachusetts has revealed that at least 50 per cent of adults have no demonstrable antitoxin in the blood. The commonest portal of entry for the diphtheria bacillus is the upper respiratory tract. The organism may, however, also invade the skin, genital tract, eye or the middle ear. The incubation period is 2 to 4 days, but may be as short as one or as long as 7 days.

The systemic reactions in uncomplicated diphtheria are, as a rule, of only minor to moderate severity. Although fever is present, it is usually of low degree, 100° to 101°F. When toxic manifestations are absent, patients feel quite well except for mild discomfort in the pharynx. In those in whom the toxin exerts its effects, pallor, listlessness, tachycardia, and weakness are striking. In the terminal stages of the disease, peripheral vascular collapse is common.

The very early diphtheritic membrane in the pharynx often consists of small areas of soft exudate which resemble

from 5 to 6 weeks after infection and may persist for a year or more; it is protective only against the serological type which provoked its production and is ineffective against all other types. Therapy with penicillin or Aureomycin depresses the formation of antistreptolysin, antistreptokinase and antibacterial antibody.

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ing. Involvement of the trachea or larynx, or both, leads to occlusion of the airway with the development of progressive respiratory difficulty which may terminate fatally unless tracheotomy or intubation is carried out. In some cases, the membrane extends into the bronchial tree and produces diffuse bronchopneumonia in which severe air hunger is striking. As a rule, little or no sputum is produced until the bronchial membrane separates and breaks up. Bronchopulmonary diphtheria is very serious not only because of the presence of obstruction but also because a large surface

theria may rarely be limited to the larynx or trachea, without involvement of the pharynx. This possibility must always be kept in mind in the differential diagnosis of "croup".

Studies based on electrocardiographic observations have suggested that myocarditis occurs in about two-thirds of patients with diphtheria. On the basis of clinical findings alone, approximately 10 per cent have cardiac involvement, in these, bundle branch block, incomplete or complete heart block, auricular fibrillation, ventricular extrasystoles or tachycardia or both, or alterations in the heart sounds are detectable. In the remaining 90 per cent, physical examination is unrevealing, but ECG tracings show abnormal T waves or S-T segments, or prolongation of auriculo-ventricular conduction time. The fatality rate varies with the intensity of the electrocardiographic and physical changes; it is approximately 90 per cent in patients with severe heart involvement and about 5 per cent in those in whom only minor ECG alterations are detectable. Diphtheritic heart disease is not "benign" despite the fact that many individuals survive it; fibrosis of the myocardium has been observed in persons who have died several weeks after having had minor electrocardiographic abnormalities.

the follicular pharyngitis or tonsillitis observed in streptococcal and some viral infections. It is easily wiped off and leaves no bleeding. As the disease progresses, this pseudomembrane coalesces to form a thin sheet which may cover the tonsils or posterior pharyngeal wall, or both, and is easily removed. Later, it becomes more dense, is white, gray, or black in color depending on the degree of hemorrhage, and is firmly attached to the underlying mucous membrane so that, when it is detached, bleeding spots are visible. There is usually a small area of inflammatory reaction about the periphery of the membrane. If there is mixed infection, with the beta-hemolytic streptococcus for example, the pharynx is diffusely red and edematous. In the average case, there is very little soreness of the throat; severe discomfort may be present in some cases. There is only a moderate degree of leucocytosis, usually not over 15,000 white blood cells per mm^3.

The membrane may spread to cover completely the pharynx, tonsils, and soft and hard palates. Patients with severe disease may present the picture of so-called "malignant" diphtheria. This is characterized by marked swelling of the submandibular areas and anterior neck, producing the typical "bull neck". The breathing is noisy and carried on through the open mouth, the breath foul, and the speech thick. The pharyngeal tissues are red and edematous, and the lymph nodes in the cervical region are enlarged. The skin is pale and cool. There is great weakness. Occasionally, purpuric eruptions of the skin may appear, particularly in the region of the neck and the anterior chest wall. Varying degrees of drowsiness and delirium are not uncommon.

The complications of diphtheria are of two types; those which result from spread of the faucial membrane into the respiratory tract and those which are produced by the absorption of exotoxin.

With extension of the pharyngeal exudate into the lower respiratory tract, there is gradual interference with breath-

exudate increases for about a week and then gradually disappears when specific therapy is not given. The fatality rate in patients who do not receive antitoxin is about 35 per cent; it is as high as 90 per cent when laryngeal involvement is present. The time of administration of antitoxic serum is important in determining the outcome; 1.5 per cent of cases are fatal when antitoxin is given on the first day, while 20 per cent die if treatment is delayed for 5 days. The location of the disease and the type and severity of complications are also important in prognosis. Infection of the anterior portion of the nose may be present for many months without producing any toxic manifestations. This is also true of skin diphtheria, although, in some instances, symptoms and signs resulting from absorption of toxins may appear after many weeks.

The presence of diphtheria is usually suspected when a membrane having the features described above is observed in the pharynx. It must be emphasized, however, that the exudate in the pharynx is not always typical and there are a number of other infections in which pseudomembranes appear with which it may easily be confused. Among these are the infectious mononucleosis, streptococcal pharyngitis, viral exudative pharyngitis, fusospirochetal angina, acute moniliasis, and staphylococcal infections of the throat secondary to chemotherapy.

The only positive method of establishing the diagnosis of diphtheria is by demonstrating typical *C. diphtheriae* in stained smears and cultures of the membrane. With some experience, it is possible to make a positive diagnosis on the basis of methylene-blue stained smears in 75 to 85 per cent of cases. Such observations must always be confirmed by the isolation of the organisms. In patients who have received no chemotherapy, the bacteria grow out on Loeffler's medium after only 8 to 12 hours of incubation. If antibiotics, especially penicillin, have been given prior to bacteriologic study, as long as 5 days may be required before the cul-

In addition to arrythmias and sometimes in their absence, cardiac failure may develop during the course of diphtheria. The right side of the heart usually fails first. Pain in the right upper quadrant of the abdomen is often the first symptom; this results from rapid enlargement of the liver due to acute congestion. Basal pulmonary rales are present in some cases.

Peripheral neuritis occurs at different times in the course of diphtheria. In severe cases, paralysis of the soft palate and posterior pharyngeal wall *may appear very early;* this is probably due to direct action of the toxin on the pharyngeal motor nerve endings. More frequently (10 per cent), *neuritis develops during the second to the sixth week.* The cranial nerves are the ones most often involved, dysfunction of N III, VI, VII, IX, and X being most common. Any of the peripheral nerves may, however, be affected and paralysis of the extremities, diaphragm, or intercostal muscles has been observed. Most striking is motor loss; sensory changes are usually uncommon and, when present, are of only mild degree. In a few instances, peripheral neuritis may not occur until 2 to 3 months after the onset of diphtheria; the clinical picture and course resemble infectious polyneuritis. The outstanding findings are symmetrical decrease of sensation in a glove and stocking distribution, and albumino-cytologic dissociation in the cerebrospinal fluid identical to that present in the Guillain-Barre syndrome. Motor loss and areflexia develop if the disease progresses. Complete recovery is usual, although this may require as long as a year. Death occurs occasionally in those with the most extensive involvement.

Rarely, often without warning, peripheral vascular collapse develops suddenly in diphtheria. The mechanism of this complication is not known. Death usually occurs rapidly, despite intensive therapy for shock.

In mild cases of untreated faucial diphtheria, the membrane may disappear in 3 to 4 days. In the average case,

because of great danger of death from anaphylactic shock.

Antitoxin must be given as early in the course of diphtheria as possible. Delay in treatment increases the incidence of complications and death. It has been suggested that larger quantities of antiserum are necessary when therapy is given late. However, since toxin is fixed instantaneously to tissues and then cannot be neutralized by even the most massive doses of antitoxin, the beneficial effect of increasing the amount of antiserum is highly questionable. The diphtheritic membrane frequently increases in size for 24 hours after the administration of antitoxin; this does not indicate too small a dose or the need for additional serotherapy.

Chemotherapy has no effect in altering the clinical course of diphtheria. The incidence of complications and death is the same in patients who receive antibiotic plus antitoxin as in those who are given only antiserum Penicillin, however, rapidly eradicates the carrier state; 40,000 units of crystalline penicillin given intramuscularly every 4 hours for 12 days has been found to rid the pharynx of diphtheria bacilli in practically 100 per cent of cases. A single daily injection of 600,000 units of procaine penicillin or erythromycin (250 mg. orally every 6 hours) for 12 days produce the same result. It has been suggested that Aureomycin or Terramycin may also be effective.

In obstruction of the larynx due to diphtheria, intubation or tracheotomy may be necessary. Not much can be done to alter the course of diphtheritic myocarditis; quinidine has been used in an attempt to manage some of the arrhythmias, but little has been accomplished. Procaine amide (Pronestyl) may be of value in ventricular tachycardia in this disease, but no experience with it has been reported. Many investigators are of the opinion that digitalis is completely contraindicated in congestive heart failure in diphtheria and recommend restriction of fluids and salt and the administration of diuretics. Others, however, feel that digitalis may be

ture becomes positive, or they may remain completely negative; it is often impossible to demonstrate the bacilli in direct smears from the pharynx in such cases. All strains of *C. diphtheriae* are not virulent. In order to establish the causal relationship of the organism to the disease, it is necessary to demonstrate toxin formation. This is accomplished by injecting a small quantity of a culture of the suspected strain into the skin of two guinea pigs, one of which has previously been given antitoxin. A positive reaction in the unprotected animal and a negative one in the protected one establishes the toxigenicity of the bacteria. An *in vitro* method for demonstrating production of toxin is also available.

The only specific treatment for diphtheria is antitoxin. Although the dosage schedules are empiric, experience dictates the use of certain quantities in specific situations. Antiserum must never be given until tests for sensitivity to horse serum have been carried out. If the eye and skin reactions are negative after 20 to 30 minutes, antitoxin may be given freely; even in the absence of demonstrable hypersensitivity, it is probably best to administer the antiserum in divided doses to adults. The following dosage schedule is widely used; when membrane is present on only one tonsil, 5,000 units of antitoxin are given, and for a lesion covering both tonsils, 10,000 units. When the entire pharyngeal wall and the tonsils are involved, the quantity is increased to between 20,000 and 50,000 units. In laryngeal diphtheria, it is best to inject 50,000 to 100,000 units of antitoxin. Because of the length of time required for serum administered intramuscularly to reach its highest level in the circulating blood, one-half of the dose should be administered by this route. About one hour later, the remainder is given intravenously, if no reaction has occurred. Desensitization must be carried out in individuals highly reactive to horse serum. The degree of hypersensitivity may be so great rarely that serotherapy cannot be accomplished

antimicrobial therapy, it was very difficult or impossible to eliminate the carrier state. This can now be readily accomplished, however, by the administration of penicillin or erythromycin, as described above; if bacteriologic relapse occurs, a second course of therapy usually results in complete eradication of the organisms.

H. Influenzae Pharyngitis and Epiglottitis

Pharyngitis due to *H. influenzae* is much more common in children than in adults. It is not characterized by any specific features which allow its etiology to be established on clinical grounds alone. The pharyngeal mucous membrane is reddened; the lymphoid follicles may be enlarged. Rarely, a small amount of yellow exudate is detectable. The only method of establishing the diagnosis of influenzal sore throat is by demonstration of the typical gram-negative pleomorphic bacilli in gram-stained smears and throat cultures. Tetracycline and chloramphenicol are effective therapy. The dose of these drugs is 0.25 gm orally every 6 hours. Treatment should be continued for 7 days.

Acute epiglottitis in children is most often due to *H. influenzae*. The pneumococcus may also be responsible for this infection, especially in adults. The outstanding symptoms are pharyngeal discomfort and difficulty in breathing. Physical examination usually reveals inflammation of the pharynx and a red, markedly edematous epiglottis which is so enlarged in many cases that it is easily seen when the tongue is depressed. The diagnosis of this disease is readily made when the inflamed epiglottis is visualized. Treatment should be initiated immediately. Either chloramphenicol or tetracycline, 50 to 75 mg. per Kg , in 4 equally divided doses per day, is effective not only in the cases due to the influenza bacillus but also in those produced by the pneumococcus, although penicillin is the drug of choice when this organism is present. Children with acute epiglottitis must be watched constantly for evidence of respiratory obstruc-

used with safety and with beneficial effect in this situation. This question remains unsettled. There is no therapy for the peripheral neuritis.

Diphtheria is, for the most part, a preventable disease. The administration of alum-precipitated toxoid at the age of 3 to 6 months must be a routine procedure. "Booster" doses should be given at the age of one year and again just before a child goes to school. Adults should be included in the immunization program. Although it has been suggested that Schick testing is not necessary in those who have received toxoid, many physicians still rely on this test to indicate the absence or presence of protection. In addition, a Schick test acts as a "booster". Rarely, a serious local or systemic reaction may follow the endermal injection of the toxin. Although most school children are immune to diphtheria, adults are, on the whole, susceptible. A recent study has indicated that over 50 per cent of the adult population in Massachusetts has no demonstrable diphtheria antitoxin in the blood. Until recently it has been virtually impossible to give adults diphtheria toxoid because of the high incidence of severe constitutional reactions. The availability of highly purified preparations of toxoid has minimized the risk of untoward sequelae, and made immunization of individuals in all age groups practical. A small number of immunized persons, even those with negative Schick reactions, may still develop diphtheria. A recent study of 200 cases of this disease revealed negative skin tests in 15 per cent; although some of the patients showed complications, none died.

Individuals exposed to a known case of diphtheria who have never been actively immunized should receive 5,000 units of antitoxin; such passive protection lasts for about 2 weeks. In those who have previously received toxoid, a "booster" dose of this material is usually sufficient to protect them against development of the disease.

Many cases of active diphtheria are contracted from asymptomatic carriers. Until the development of effective

indicated that specific viruses may frequently be responsible for infections of the throat which may become epidemic. The adenoviruses (adenoidal-pharyngeal-conjunctival, or APC group) and Coxsackie viruses are examples; these are discussed below. There are other pharyngitides, however, *from which viral agents or pathogenic bacteria have not* been isolated and in which the outstanding manifestation is pharyngeal exudate. This type of disease is often confused with streptococcal sore throat. In general, there is less constitutional reaction and fever, the exudate is not as intense, and the inflammatory reaction and edema in the pharynx are less marked than when streptococcal infection is present. In individual patients, however, it is often very difficult to rule out streptococcal pharyngitis, especially the mild form, on the basis of these criteria. The white blood count is usually normal. Viral exudative pharyngitis is a benign, uncomplicated, self-limited disease. There is no specific treatment; antibiotics are without effect.

Adenovirus (Adenoidal-Pharyngeal-Conjunctival, APC) Pharyngitis

A new group of viruses responsible for sporadic and epidemic cases of pharyngitis, as well as "viral pneumonia" and keratoconjunctivitis, has recently been isolated. These agents are closely related or identical to the viruses ARD and RI67, which have been demonstrated in cases of undifferentiated upper respiratory infections

The adenoviruses are very widespread and probably a common cause of pharyngitis. Fever is present in about 80 per cent of cases, may be as high as 103° to 104° and persist for as long as 10 days. Most patients have a sore throat which is often very mild. Physical examination usually reveals only mild reddening or injection of the pharynx and enlargement of the lymphoid tissue. As a rule, there is nontender submaxillary lymphadenopathy. Conjunctivitis is present in the majority of cases and lasts, as a rule, for only

tion, and tracheostomy carried out as soon as it appears that the occlusion of the airway cannot be relieved by any other method.

Hemophilus hemolyticus, an organism related to *Hemophilus influenzae*, may rarely produce pharyngitis. The two types of disease cannot be differentiated clinically. The two organisms are distinguished by the fact that *H. hemolyticus* colonies on blood agar are surrounded by a clear zone of complete hemolysis. It must be kept in mind that this species is not infrequently a component of the normal microbial flora of the throat. The treatment is the same as that for disease produced by *H. influenzae*.

Staphylococcus Aureus Pharyngitis

Staph. aureus is commonly present in the throat of normal individuals. It is rarely, if ever, a primary cause of pharyngitis. In some individuals who have been receiving antibiotics, especially the "broad spectrum" drugs, thick exudate appears on the pharynx and tonsils and a membrane resembling closely that present in diphtheria develops. Although this may be due to yeast infection in some cases, in a few the only organism which can be isolated is a coagulase-positive hemolytic *Staph. aureus*. The diagnostic difficulty in this situation is attaching causal significance to the staphylococci since they are so frequently present normally. It has been the writer's practice to treat this syndrome after it has been proved not to be due to diphtheria, infectious mononucleosis, or mycotic infection, and *Staph. aureus* is the sole organism present in a patient with fever and leucocytosis. The therapy used has been 0.25 to 0.5 gm. of chloramphenicol plus the same quantity of erythromycin given orally every 6 hours for 7 to 10 days.

Viral Exudative Pharyngitis

Not all cases of acute pharyngitis in which exudate is present are due to bacterial invasion. Recent studies have

indicated that specific viruses may frequently be responsible for infections of the throat which may become epidemic. The adenoviruses (adenoidal-pharyngeal-conjunctival, or APC group) and Coxsackie viruses are examples; these are discussed below. There are other pharyngitides, however, from which viral agents or pathogenic bacteria have not been isolated and in which the outstanding manifestation is pharyngeal exudate. This type of disease is often confused with streptococcal sore throat. In general, there is less constitutional reaction and fever, the exudate is not as intense, and the inflammatory reaction and edema in the pharynx are less marked than when streptococcal infection is present. In individual patients, however, it is often very difficult to rule out streptococcal pharyngitis, especially the mild form, on the basis of these criteria. The white blood count is usually normal. Viral exudative pharyngitis is a benign, uncomplicated, self-limited disease. There is no specific treatment; antibiotics are without effect.

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The adenoviruses are very widespread and probably a common cause of pharyngitis. Fever is present in about 80 per cent of cases, may be as high as 103° to 104° and persist for as long as 10 days. Most patients have a sore throat which is often very mild. Physical examination usually reveals only mild reddening or injection of the pharynx and enlargement of the lymphoid tissue. As a rule, there is nontender submaxillary lymphadenopathy. Conjunctivitis is present in the majority of cases and lasts, as a rule, for only

a few days, although it may be present for 3 weeks; it is usually unilateral and is characterized by mild injection of the bulbar and palpebral conjunctivae and ipsilateral preauricular lymphadenopathy. *Exudate in the conjunctival* sac is very rare and, when present, usually serous. Headache is common, and muscle, bone, and joint aching occurs occasionally; these may cause confusion with influenza. The incubation period is from 5 to 10 days. The disease is more common in children than in adults; in the older age group, it is more frequent in women than men. The period of communicability is about 9 days after invasion takes place.

The possibility of pharyngitis due to the adenoviruses is suspected in patients with a sore throat and unilateral conjunctivitis. The established presence of the disease in a family or community is of epidemiologic help. The definitive diagnosis can be made on the basis of serologic tests; these are at present available, however, only in research laboratories. There are no effective methods of treatment. A vaccine containing *several serotypes* of the virus has been shown experimentally to produce protection against invasion by the agents which it contains.

Infectious Mononucleosis

Although the specific causative agent of infectious mononucleosis has not been isolated or identified, it is probably a virus. The disease is transmitted by way of the respiratory tract. *Kissing has recently been implicated as the most common* mode of spread of this infection.

Approximately 75 to 90 per cent of patients with infectious mononucleosis have a sore throat. The appearance of the pharynx is variable. In some cases, only mild *injection* of the mucous membrane is apparent. In others, there is marked redness and edema, and the lymphoid tissue is swollen. A membranous pharyngitis very difficult to distinguish from diphtheria or an ulcerative process due to fusospirochetal infection is present in some instances; the latter

occurs most often when there is marked leukopenia. Very rarely, pharyngeal diphtheria and infectious mononucleosis may occur simultaneously; for this reason cultures for *C. diphtheriae* must be made in all cases in which membrane appears in the throat.

Lymphadenopathy is the rule in infectious mononucleosis. Only a single lymph node may be involved, or the process may be generalized. Splenomegaly is very common, but may be absent throughout the entire illness in a small number of cases. Various types of skin eruptions may appear and cause confusion with measles, scarlet fever, rubella, and diseases in which petechial and purpuric rashes are present. Hepatic dysfunction, as determined by excretion of bromosulfalein, is detectable in most patients in the early phase of infection. Severe liver involvement with jaundice, biliuria, hepatomegaly, and laboratory evidence of hepatocellular damage occurs in some, the syndrome cannot be differentiated clinically from infectious hepatitis. Hematuria is occasionally observed. Edema of the upper eyelids is common. Pneumonia, indistinguishable from "atypical viral pneumonia" occurs in 10 per cent of cases. Meningitis or severe meningoencephalitis develops infrequently, the number of cells in the spinal fluid is increased, and "atypical lymphocytes" are sometimes noted. Peripheral neuritis may appear. Pleural effusion has been reported in one patient. A significant degree of anemia is uncommon.

The diagnosis of infectious mononucleosis is usually suspected clinically when pharyngitis, lymphadenopathy, and splenomegaly are detected in individuals who have "atypical lymphocytes" in the peripheral blood smear. The same type of cell may be observed, however, in infectious hepatitis, measles, and other viral exanthemata. In the early stages of the disease, the white blood count is often elevated with an increase in neutrophiles; it may be as high as 50,000 to 60,000 per mm^3. In some cases, there is leukopenia, the number of cells being as low as 2,000 to 3,000 with 70 to

80 per cent lymphocytes, many of which are "atypical". Proof of the presence of infectious mononucleosis rests on the demonstration of a significant titer of "heterophile antibody" in the serum. This test is positive in 95 per cent of patients; 7 to 8 weeks may be required, in some instances, before the titer reaches a diagnostic level. Infections with certain bacteria or the administration of horse serum also produces a positive reaction. Many people have a "normal" heterophile agglutinin. The Davidsohn exclusion test differentiates the 3 types of antibody. The one resulting from the injection of horse serum is removed by contact with guinea pig kidney or beef erythrocytes. "Normal" heterophile agglutinin is absorbed by guinea pig kidney but not by beef erythrocytes; the opposite is the case in infectious mononucleosis. A diagnostic titer of heterophile antibody in infectious mononucleosis is 1·128 or higher; a level of 1:64 is suggestive. Most significant is the demonstration of an increase in antibody when convalescent and acute phase serums are compared. Heterophile agglutination indistinguishable from that of infectious mononucleosis appears with lymphoma or lymphosarcoma, very rarely. A helpful point in distinguishing these is the progressive development of anemia when Hodgkin's disease is present.

Infectious mononucleosis is usually a benign disease, and complete recovery is the rule. Recrudescence is not rare, however. In some cases, manifestations persist for 2 to 3 months. Patients with severe hepatitis may be ill for 3 months or longer. Death is very rare; it has followed rupture of the spleen or severe meningoencephalitis. "Atypical" lymphocytes may be present in the peripheral blood, and the lymph nodes remain enlarged for a long time after the acute disease.

There is no specific therapy for infectious mononucleosis. Antibiotic agents do not exert a favorable effect on the disease unless there is secondary bacterial infection of the

pharynx. In the rare case in which virulent diphtheria bacilli are isolated from the throat, treatment for diphtheria as described above must be instituted.

Herpes Simplex Stomatopharyngitis

The first exposure to the virus of herpes simplex may lead to the development of a severe vesicular pharyngitis and stomatitis in some patients. This occurs most often in young children, but appears rarely even in adults who come in contact with the virus for the first time. Fever which may be as high as 105°F. and generalized aching are common symptoms. Pain in the mouth and throat are often so intense that chewing and swallowing are difficult. Examination reveals multiple vesicles of different size on the buccal mucous membrane, pharyngeal wall and tongue. The lesions contain clear fluid and are surrounded by a small zone of inflammatory reaction. They rupture early and leave shallow ulcerations which are covered by thin, white or gray, pseudomembrane. The white blood count is usually normal. Despite the severity of the illness, practically all patients recover. The only important complication is encephalitis which occasionally produces death.

The diagnosis of herpes simplex stomatopharyngitis may be suspected when a vesicular pharyngitis is present in a patient with a history of recent exposure to a "fever blister"; the contact is often by way of kissing, drinking from a common glass, or, in very young infants, suckling at the breast which is the site of a localized herpetic infection. The diagnosis is specifically established by demonstration of a rising neutralizing antibody titer for herpes simplex virus The disease does not respond favorably to any antibiotic agents.

Sore Throat in Syphilis

Sore throat may appear in secondary syphilis. It is usually a component of the generalized mucous membrane involve-

80 per cent lymphocytes, many of which are "atypical". Proof of the presence of infectious mononucleosis rests on the demonstration of a significant titer of "heterophile antibody" in the serum. This test is positive in 95 per cent of patients; 7 to 8 weeks may be required, in some instances, before the titer reaches a diagnostic level. Infections with certain bacteria or the administration of horse serum also produces a positive reaction. Many people have a "normal" heterophile agglutinin. The Davidsohn exclusion test differentiates the 3 types of antibody. The one resulting from the injection of horse serum is removed by contact with guinea pig kidney or beef erythrocytes. "Normal" heterophile agglutinin is absorbed by guinea pig kidney but not by beef erythrocytes; the opposite is the case in infectious mononucleosis. A diagnostic titer of heterophile antibody in infectious mononucleosis is 1:128 or higher; a level of 1:64 is suggestive. Most significant is the demonstration of an increase in antibody when convalescent and acute phase serums are compared. Heterophile agglutination indistinguishable from that of infectious mononucleosis appears with lymphoma or lymphosarcoma, very rarely. A helpful point in distinguishing these is the progressive development of anemia when Hodgkin's disease is present.

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marked preponderance of fusiform organisms and spirochetes. Cultures are not practical because of the technical difficulties involved in growing the highly anaerobic fusiform bacilli. Careful judgement must be exercised in establishing a causal relationship between the bacteria observed in smears and the disease because a small number of these organisms are always present in the throats of normal persons.

The treatment of choice for fusospirochetal pharyngitis is penicillin. In moderately severe cases, the injection of 600,000 to 1,200,000 units of procaine penicillin daily for 10 days produces complete cure. If the infection is very severe and the constitutional reaction marked, hospitalization is desirable; in such instances, it is best to administer 250,000 to 500,000 units of crystalline benzyl penicillin G intramuscularly every 4 to 6 hours for 10 days. Good results have been produced in mild infections with chlortetracycline (Aureomycin); a dose of 0.25 to 0.5 gm. orally every 6 hours for 10 days is adequate.

Mycotic Infection of the Pharynx

Moniliasis of the buccal mucous membrane, throat and tongue (thrush) is relatively common in neonatal children born to mothers with vaginal moniliasis; the infection is very superficial in these cases. Discrete patches of white "exudate" on the mucous membranes is the characteristic finding. The disease is readily curable by irrigating the mouth and throat with sterile water. In older individuals, moniliasis of the pharynx may occur during the course of acute or chronic debilitating systemic conditions. At present, the most common cause of this type of infection is the administration of antibiotics, especially the "broad spectrum" drugs, which results in suppression of other organisms in the throat and overgrowth and invasion by *Monilia* (*Candida*). The lesions are often numerous and widely distributed in the mouth and pharynx. They are painful, shallow

ment that occurs in this stage of the disease. The pharynx may be only mildly injected, or "mucous patches" of the same type as are present on the buccal mucous membrane or tongue may be observed. The possibility of syphilitic pharyngitis should be suspected in any case of prolonged pharyngeal discomfort or when lesions suggestive of "mucous patches" are detected. The diagnosis is confirmed by serologic tests and dark-field examination of the lesions in the throat. The treatment is that of other forms of syphilis.

Fusospirochetal (Vincent's) Angina

Fusospirochetal pharyngitis occurs most commonly in individuals with underlying localized or systemic disease. Thus, it is often secondary to fusospirochetal gingivitis (trench mouth), local injury in the pharynx, agranulocytosis, leukemia, or infectious mononucleosis. It may also be observed, however, in normal individuals. In severe cases of Vincent's angina, the temperature may be markedly elevated, the white blood count high, and the patient may appear severely ill. With milder infections, the constitutional reaction is less marked, and the chief complaint is of sore throat. Examination of the pharynx usually reveals a number of ulcers of varying size the bases of which are covered by gray, necrotic pseudomembrane which may cause bleeding when removed. The breath has a distinctive foul odor resembling rancid butter and characteristic of anaerobic bacterial growth.

In most instances, no complications develop. In a rare case, however, extensive necrosis of the pharyngeal tissue may occur and result in loss of the tonsils, soft palate or parapharyngeal structures with erosion into the internal carotid artery and death by exsanguination. The infection may spread from the pharynx to the lungs or genitalia.

The diagnosis of fusospirochetal angina is made on the basis of the appearance of the pharyngeal lesion and the demonstration, in gram-stained smears of exudate, of a

marked preponderance of fusiform organisms and spirochetes. Cultures are not practical because of the technical difficulties involved in growing the highly anaerobic fusiform bacilli. Careful judgement must be exercised in establishing a causal relationship between the bacteria observed in smears and the disease because a small number of these organisms are always present in the throats of normal persons.

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ulcers covered by heaped-up white exudate. Fever and constitutional reaction are slight or absent.

The diagnosis of *Candida* pharyngitis is suggested by the appearance of the lesions. It is established by demonstrating the organisms in stained smears or in cultures on Saboraud's medium. It must be stressed, however, that the mere presence of *Monilia* in a culture or smear does not prove that it is responsible for the disease because this organism is present in the throats of normal individuals.

The treatment of choice for monilial pharyngitis is the application of one per cent gentian violet to the lesions twice a day. It has recently been suggested that irrigation with solutions of Nystatin (Mycostatin) is also effective.

The "Common Cold"

The "common cold" is an acute, epidemic respiratory infection. The etiology is unknown, but the clinical and epidemiologic features are consistent with a viral disease. This syndrome may be produced by some specific viruses or by irritative or allergic factors and cause considerable diagnostic confusion. Extraneous factors do not produce the disease. Experimental studies have shown, for example, that chilling is not responsible for the "common cold", although it may cause nasal obstruction and pharyngeal discomfort. A patient carrying the agent of the "common cold" may be more susceptible to invasion by the "virus" if subjected to chilling or over-heating, however.

The "common cold" becomes epidemic during 3 periods of the year; September and October, January and February, and April and May. The largest number of cases appears in the winter. The disease is mildest in the spring.

The symptoms of the "common cold" are coryza, rhinorrhea, nasal obstruction, and sneezing. The nasal discharge is at first thin and copious, and then becomes more viscous and, not infrequently, purulent. Fever and cough are uncommon. The white blood count is normal. The disease is

self-limiting and usually lasts only 1 to 2 days, although manifestations may persist for as long as 2 weeks. Most important are the complications which occur. These are due to secondary bacterial invasion and include acute otitis media, purulent sinusitis, and pneumonia.

The diagnosis of the "common cold" is very difficult to make with certainty because of the other conditions with which it may be confused. Differentiation from vasomotor or allergic rhinitis or nasal obstruction due to chemical or mechanical irritation, for example, may be impossible. There are no specific serologic tests.

There is no specific therapy. Antihistaminic drugs are useless. The antibiotics are of no value. Prophylaxis with antimicrobial agents does not decrease the risk of secondary bacterial infection and should not be employed, because the organisms which may be responsible for complications occurring when these drugs are being given are often insensitive and very difficult or impossible to eradicate. Commercially available "cold vaccines" are totally ineffective in preventing the "common cold". Avoidance of overcrowding and contact with individuals with "colds" is the best prophylactic measure.

Viral Influenza

There are 3 main serologic types of virus—A, B, and C; several antigenic variants of types A and B have been responsible for infection. The most recent epidemic of influenza (1957) has been found to be due to a variant of type A virus immunologically distinct from other mutants of this type. This epidemic started in Northern China and then spread over the Orient producing a large number of cases in China, Formosa, Philippines, Singapore, Malaya, Indonesia, Japan, and India; for this reason it has been referred to as "Asiatic" or "Oriental flu". At the time of writing of this book, epidemic foci of the same type of infection are being reported from various areas in the United

States and Europe. There is a certain epidemic periodicity associated with the specific serotypes. For example, type A is responsible for epidemics every 2 to 3 years, while type B is involved in large outbreaks about every 4 to 5 years. The attack rate is usually very high; 20 to 30 per cent of non-immune contacts contract influenza once it appears in a community. There are always more inapparent than clinically recognized infections.

There is no cross immunity between the different types of influenza virus. For example, a patient recovered from infection with type A may have a second attack due to type B. The incubation period of influenza is 12 to 48 hours. The onset is abrupt. Many patients can state the exact hour at which they became ill. *The first manifestations may be* syncope and collapse. Mild to moderate prostration, fever as high as 105°, generalized muscle and bone pain, backache and headache occur in more than 60 per cent of cases. Pain on movement of the eyes is frequent. Nasal discharge, dry cough, reddening of the conjunctivae and sore throat are common. Among the uncommon manifestations (less than 20 per cent) are very severe prostration, nausea, vomiting, diarrhea, and abdominal pain. Physical examination reveals a severely ill, prostrated, febrile patient. Bradycardia relative to the degree of elevation of the temperature is usual. The face is flushed, and there is a varying degree of conjunctivitis. The mucous membrane of the nose and pharynx are red and edematous and, in severe cases, the site of multiple punctate hemorrhages; epistaxis is not unusual. Cyanosis may appear in some instances. In most cases the lungs are normal; in some, there may be occasional rales or rhonchi. The spleen is often palpable. The white blood count is usually depressed, although leucocytosis may be present. Symptoms persist for about 3 to 5 days. The complications of influenza result from secondary bacterial invasion and are infrequent. Sinusitis, otitis media, and pneumonia may occur

and be due to *Staph. aureus;* pulmonary involvement may, however, be produced by the influenza virus itself. Myocarditis and heart failure leading to death is a rare complication.

Marked asthenia is practically always present during convalescence from influenza. Weakness and easy fatiguability may be striking for as long as a month or more. The fatality rate in epidemic or sporadic influenza is very low. Death occurs most often in elderly individuals or when complications develop.

The diagnosis of influenza is usually made on clinical grounds. The presence of generalized aching, some degree of prostration, sore throat, multiple punctate hemorrhages in the nasal mucous membrane, high fever, leukopenia, and bradycardia suggest the possibility of the disease. Serologic studies establish the presence of the infection, usually in retrospect. Since the influenza virus agglutinates red blood cells, the demonstration of a minimum of a four-fold increase in the anti-hemagglutinin titer of acute and convalescent phase serums is diagnostic.

Chemotherapy does not alter the course of influenza. The administration of chemoprophylaxis is questionable. Because of an increased susceptibility to secondary infection of the lungs by *Staph. aureus,* particularly in epidemic cases, however, it has been suggested that 600,000 units of procaine penicillin be given daily. Proof for the effectiveness of this measure is still lacking; the possibility of invasion by antibiotic-resistant organisms must be kept constantly in mind. The writer prefers to withhold drugs.

Influenza may be prevented by a single injection of inactivated viral vaccine in about 60 to 85 per cent of patients; immunity lasts for about 6 to 9 months. The vaccine produces severe constitutional reactions with fever, headache, generalized aching and nausea and vomiting in some individuals. The main drawback to the practical application of

this material, however, is the fact that an epidemic may be due to a serological type of virus which is not present in the vaccine. When an outbreak of the disease occurs, it is imperative that the responsible serotype be isolated and identified as rapidly as possible. If it is different than the ones present in the available vaccine preparation, it should be included promptly in order that immunization may be most effective.

Coxsackie Virus Infection

Infection with group A Coxsackie virus produces herpangina. This is an epidemic disease which involves primarily children but may also affect adults. The manifestations are limited to the pharynx, examination of which reveals a cluster of 6 to 8 or 10 vesicles usually in one area on the soft palate. There are no other abnormal physical findings except for a moderate degree of fever. The white blood count is normal. The disease lasts for 4 to 5 days to a week or longer, and recovery without complications or sequelae is the rule. The diagnosis is confirmed by demonstration of a rising antibody titer for group A Coxsackie virus in acute and convalescent serums. There are no specific methods of prevention or treatment.

CHAPTER VII

INFECTIONS OF THE LOWER RESPIRATORY TRACT

Infections of the Larynx and Trachea

Acute laryngitis and tracheitis are usually secondary to or accompany infections of the upper respiratory tract; bronchial involvement is often also present. The infectious agents most frequently responsible for this type of disease are the same as those which produce pharyngitis most commonly (Chapter VI). The outstanding manifestations of laryngotracheitis result from inflammation, edema, and narrowing of the lumen of these structures and include cough, pain and tenderness over the larynx and trachea, "croupy" breathing, and wheezing. These vary considerably in severity, and all are not present in every case. Fever of varying degree and malaise are common. In some cases, especially children who are not treated or in whom therapy is ineffective, signs of obstruction of the airway may appear and progress with startling rapidity. At first, there is only wheezing inspiration. This is usually followed by inspiratory stridor or "croup". With more marked occlusion, tachypnea, dyspnea, dilatation of the alae nasi, increasing restlessness, use of the accessory muscles of respiration, and retraction of the ribs and lower sternum appear. In the most advanced stage, cyanosis, lethargy, stupor, and finally coma are striking before death takes place. The possibility of a foreign body in the airway must be ruled out in every instance. In

very young babies, severe pneumonia or bronchiolitis without laryngeal or tracheal obstruction may be accompanied by inspiratory retraction of the ribs and lower sternum, wheezing, dyspnea, and use of the accessory muscles of respiration. Laryngospasm due to rickets may also produce the syndrome. Among the other conditions which must be considered when manifestations of airway occlusion are present are congenital abnormalities of the vascular tree (rings crossing or enclosing the trachea), laryngismus stridulus, enlarged tongue which falls back into the pharynx when a child is lying down, paralysis of the vocal cords, epiglottitis, and glottal or laryngeal spasm.

The diagnosis of laryngotracheitis is made on the basis of the characteristic signs and symptoms. The etiology is established by culture of the pharynx or of material obtained from the larynx or trachea. Most cases are due to viruses. It is most important to determine as quickly as possible, however, whether such organisms as the pneumococcus, beta-hemolytic streptococcus, or *H. influenzae* are present since they can be eradicated by antimicrobial agents. There is one form of the disease of probable viral origin in which the clinical course is sufficiently characteristic to be diagnostic. This is usually referred to as "simple croup". It occurs in young children who have previously been quite well except for a mild "cold" which has been present for 1 to 2 days. The patients waken suddenly, most often between 10 P.M. and 2 A.M., with "croupy" breathing; use of accessory muscles of respiration and cyanosis may be observed in severe cases. The symptoms usually last for about one hour and disappear spontaneously; they often recur at the same time for the next 2 or 3 nights. Older siblings have often had the same syndrome.

The treatment of laryngotracheitis is variable and depends on the nature of the infecting agent and the severity of the disease. In mild attacks, accompanied only by hoarseness and laryngeal discomfort and which a

ponent of an "upper respiratory infection", inhalation of steam and rest of the voice are often sufficient therapy. In severe laryngotracheitis, especially in children, the use of antibiotic agents must be seriously considered despite the fact that these drugs have no effect when viruses are involved. The white blood count is not helpful in distinguishing bacterial from viral infection because it may be elevated or normal in both. Because the disease often progresses rapidly and produces airway obstruction and death before its exact etiology can be determined, it is safest to assume that bacteria are responsible and to administer an antimicrobial drug. Cultures must be obtained *before* therapy is instituted. If bacteriologic studies indicate later that the agent first selected is not ideal, the most effective one must be substituted at once. Tetracycline or chloramphenicol, 50 to 75 mg. per Kg. divided into 4 doses given at 6 hour intervals, is the best initial therapy for laryngotracheitis in children because it is effective against *H. influenzae* which is the most common responsible organism in this age group. In adults, it is safest to start with 200,000 units of crystalline benzyl penicillin G intramuscularly every 4 hours. If, after all bacteriologic and other investigations have been carried out, it is apparent that a virus is concerned, chemotherapy should be stopped. Patients with difficulty in breathing should first be given a trial of exposure to cold moist oxygen or steam. If the symptoms have not improved after one to two hours, tracheotomy should be carried out. Sedatives must never be administered when restlessness is present because, by producing drowsiness or sleep, they may decrease the voluntary effort required to maintain adequate ventilation. Tracheotomy must never be delayed until cyanosis has appeared. Caution should be exercised in examining the pharynx of children who have been hypoxic for any length of time as a result of airway obstruction; the insertion of a throat stick in such cases has been reported to produce sudden cardiac standstill and death.

Tuberculous Laryngitis

When laryngitis is persistent, the possibility of tuberculous infection must be considered. This is always secondary to pulmonary involvement. The lesions first appear at the level of the vocal cords or the arytenoids in the posterior part of the larynx. Diffuse swelling or tubercle formation is present at the posterior end of one or both cords, in the arytenoid space, or in the cartilages. As the disease progresses, caseation and ulceration lead to the formation of irregular, shallow, rugged ulcers and finally to fibrosis and stenosis of the larynx.

The symptoms of tuberculous laryngitis are usually very mild. They are at first present only on awakening when the patient notices hoarseness and slight soreness in the larynx. If the lesions progress, hoarseness is present continuously, and moderate to severe cough appears. Pain is not a major feature unless invasion of the laryngeal cartilages takes place. When the epiglottis is involved, it is red and edematous and becomes deeply ulcerated. With such extensive disease, dysphonia, dysphagia and salivation are striking.

The diagnosis of tuberculous laryngitis should be suspected in any case of chronic hoarseness, but especially if pulmonary tuberculosis is present. Laryngoscopy should be performed. The demonstration of ulcers or tubercle-like structures on the posterior ends of the vocal cords or arytenoids is presumptive evidence. Etiologic diagnosis is established by demonstration of tubercle bacilli in smears and cultures in material obtained from ulcers or by the discovery of typical tubercles in biopsy specimens. Treatment is the same as for other forms of tuberculosis (Chapter VII, below).

Infections of the Bronchial Tree

Acute bronchitis may occur as an isolated disease but is present most often together with laryngotracheitis or pneumonia, or is secondary to a pharyngitis. Tl

sponsible for infection of the bronchial tree are the same as those which cause disease of the pharynx, larynx, and trachea, and some types of pneumonitis.

Cough is the outstanding manifestation of bronchitis; it may be dry or productive of varying quantities of purulent or mucoid sputum. Fever is often, though not always, present. The degree of constitutional reaction is variable and depends on the type, duration, and extent of bronchial involvement. Physical examination of the chest usually reveals rhonchi and coarse rales over the large bronchi. When the smaller radicles are involved, the rales are of finer quality; they become moist and bubbling as the secretions become less viscid during the course of the disease. Reduction in the diameter of the bronchial elements by edema and secretions may lead to poor ventilation with the development of cyanosis and expiratory wheezing. Acute bronchitis is usually bilateral. Segmental disease may be present, and produce findings which are difficult to distinguish from those of pneumonia because interstitial involvement or lobular consolidation occurs. When acute bronchitis is very severe, patients may appear as severely ill as with extensive pneumonia. Physical or roentgenographic evidence of pulmonary parenchymal involvement is absent, however.

The diagnosis of acute bronchitis is usually made on the basis of the history and physical examination of the chest. The presence of pneumonia is ruled out by x-ray study of the lungs. Cultures of the sputum must be made promptly in all cases because the choice of antibiotic therapy depends on the nature of the causative organism. When the proper drug has been selected, it should be given in adequate quantities for 7 to 10 days. Acute bronchitis is most dangerous in children; for this reason treatment should be initiated before the results of bacteriologic studies are available in this age group. Since *H. influenzae* is a very common cause of the disease, it is best to give tetracycline or chloramphenicol in the dose recommended above for laryngo-

tracheitis. In adults, on the other hand, the pneumococcus, beta-hemolytic streptococcus, and *Staph. aureus* are the organisms most frequently present. Penicillin is, therefore, the agent of first choice; 600,000 units of the procaine ester injected intramuscularly once a day is adequate except when an antibiotic-resistant strain of staphylococci is present. It must be stressed that a great many cases of acute bronchitis are produced by viruses. Antibiotics have no effect in these. The inhalation of steam or cold moist air and the administration of expectorants produce considerable relief of symptoms and are the only therapeutic measures applicable in the viral bronchitides.

Acute Laryngotracheobronchitis

Acute laryngotracheobronchitis occurs most frequently in children, although it may also be present in adults. The pneumococcus and *H. influenzae* are the commonest bacteria responsible for this disease; the latter is the etiologic agent in most youngsters. Many cases are due to undefined viruses.

Acute laryngotracheobronchitis is usually preceded by manifestations of an "upper respiratory infection" which are present for from 1 to 7 days with little or no fever or constitutional reaction. This is followed by the sudden onset of fever and cough which increases rapidly in severity. Extreme prostration and manifestations of air hunger may develop in 4 to 6 hours. A variable degree of cyanosis is common. Physical examination reveals an acutely ill child. Tachypnea and use of the accessory muscles of respiration are frequently present. Large and small rhonchi, moist or crackling rales, and asthmatic breathing are detectable. With severe airway obstruction, emphysema is the rule; the diaphragms are depressed, flattened, and move very little with respiration. Flaring of the alae nasi and grunting breathing are frequent. The temperature is 102 to 104°. There is usually leucocytosis with a relative increase in

neutrophiles when the disease is due to bacterial invasion; the number of white cells may be normal or decreased, however. It is not possible to differentiate the cases due to viruses from those produced by bacteria on the basis of the white blood count in many instances.

The course of acute laryngotracheobronchitis may be very short, death occurring 24 to 36 hours after the appearance of the first symptoms. This fulminating type of infection is observed most frequently in young children in whom *H. influenzae* is the causative organism. Treatment for this disease must be initiated as promptly as possible. Although many cases are due to viruses and are, therefore, untreatable, the physician must not rely on this possibility but proceed with therapy on the chance that bacteria which can be eradicated by drugs are the responsible agents. To do otherwise is to risk a death in a treatable disease, since a fatal termination may occur before the results of bacteriologic studies become available The writer treats acute laryngotracheobronchitis in young children in the following way: 50-75 mg. of tetracycline or chloramphenicol per Kg. is given as an initial dose and is followed by one-fourth of this quantity every 6 hours for 10 days; parenteral injection is preferred for the first 24 to 48 hours. Some clinicians prefer to administer 200,000 units of aqueous penicillin plus 125 mg. of streptomycin intramuscularly every 4 hours.

In addition to specific antibacterial therapy, it is often necessary to expose patients to cool, moist air or steam. Although it may appear that tracheotomy is indicated in many of these cases, this operation frequently does not relieve the respiratory manifestations because the obstruction is primarily in the bronchial tree. Bronchodilators have been used; their effectiveness remains to be proved.

Acute Bronchiolitis

Acute bronchiolitis is commonest in infancy. Although it usually is a component of a diffuse infection of the lower

tracheitis. In adults, on the other hand, the pneumococcus, beta-hemolytic streptococcus, and *Staph. aureus* are the organisms most frequently present. Penicillin is, therefore, the agent of first choice; 600,000 units of the procaine ester injected intramuscularly once a day is adequate except when an antibiotic-resistant strain of staphylococci is present. It must be stressed that a great many cases of acute bronchitis are produced by viruses. Antibiotics have no effect in these. The inhalation of steam or cold moist air and the administration of expectorants produce considerable relief of symptoms and are the only therapeutic measures applicable in the viral bronchitides.

Acute Laryngotracheobronchitis

Acute laryngotracheobronchitis occurs most frequently in children, although it may also be present in adults. The pneumococcus and *H. influenzae* are the commonest bacteria responsible for this disease; the latter is the etiologic agent in most youngsters. Many cases are due to undefined viruses.

Acute laryngotracheobronchitis is usually preceded by manifestations of an "upper respiratory infection" which are present for from 1 to 7 days with little or no fever or constitutional reaction. This is followed by the sudden onset of fever and cough which increases rapidly in severity. Extreme prostration and manifestations of air hunger may develop in 4 to 6 hours. A variable degree of cyanosis is common. Physical examination reveals an acutely ill child. Tachypnea and use of the accessory muscles of respiration are frequently present. Large and small rhonchi, moist or crackling rales, and asthmatic breathing are detectable. With severe airway obstruction, emphysema is the rule; the diaphragms are depressed, flattened, and move very little with respiration. Flaring of the alae nasi and grunting breathing are frequent. The temperature is 102 to 104°. There is usually leucocytosis with a relative increase in

The superimposition of acute bronchitis on chronic asthma, emphysema, pulmonary fibrosis, or bronchiectasis may produce an acute, severe respiratory syndrome which rapidly leads to suffocation and death.

Most patients who develop this type of bronchitis are between 40 and 50 years old. Males are affected more often than females. Constant or periodic cough, dyspnea on exertion or at rest, or "asthmatic" wheezing have usually been present for many years. A history of occupational exposure to dust is frequent. Underlying systemic disease such as diabetes mellitus, often uncontrolled, is commonly present.

The disease often begins with manifestations suggestive of "grippe", rhinitis, pharyngitis, or laryngitis. It may not progress beyond this point and terminate in full recovery in some cases. In others, however, dull presternal pain and soreness over the trachea and main-stem bronchi made worse by coughing may appear. Low-grade fever is common. The cough, dyspnea, or wheezing which are so frequently present prior to the onset of the acute infection usually increase in severity. The cough may suddenly become hacking, very harassing, and completely unproductive in patients who have previously been expectorating a moderate to considerable quantity of sputum. This is a very important sign since it indicates narrowing of the bronchial tree. This phase persists for only a short time. With progression of the process, there is an increase in the amount of sputum which is at first gray-white and viscid and later becomes mucopurulent. If properly treated, the disease may be halted at this point. In a few cases, the bronchial inflammation increases, and obstruction of the airway becomes more marked as the bronchi become narrower and occluded by edema and accumulated secretions. Dyspnea, cough, and cyanosis become more severe, and the patient appears critically ill. Anxiety, marked disorientation, and acute psychotic episodes are common. Dyspnea, restlessness, constant coughing, and inability to eat produce extreme exhaustion.

respiratory tract, the signs of involvement of the larynx and trachea are minor and overshadowed by those resulting from the inflammatory reaction in the small radicles of the bronchial tree. The bulk of cases of this disease are produced by unknown viruses. However, some are due to bacteria, the commonest of which is *H. influenzae;* the pneumococcus and beta-hemolytic streptococcus may also be involved.

The onset and clinical course of acute bronchiolitis are very similar to laryngotracheobronchitis. There is usually a history of a mild "cold" for a few days to a week. This is followed by the sudden onset of fever of varying degree and manifestations of severe and rapidly progressing respiratory embarrassment. Outstanding are tachypnea, dyspnea, cyanosis, and emphysema. As the disease progresses, the lungs increase in volume because of the difficulty in expiration imposed by the valve-like obstruction in the bronchioles. The diaphragms are markedly depressed and flattened and exhibit decreased movement. Hyper-resonance to percussion, a few rales, and wheezing expiration are detected on examination of the chest; the findings are identical with those present in an acute episode of asthma.

The treatment for acute bronchiolitis is the same as for laryngotracheobronchitis. It must be stressed again that antibiotics must be administered despite the knowledge that many cases are due to a virus because of the possibility that bacterial infection susceptible to the effect of an antimicrobial agent may be present and produce rapid death. Tracheotomy is of no help in relieving the manifestations of respiratory obstruction.

Bronchitis Superimposed on Chronic Pulmonary Disease

Bronchial infection occurring in patients with chronic pulmonary disease produces manifestations which are quite different than those which appear when bronchitis develops in normal individuals. This is a problem primarily in adults.

bronchi by means of a rubber catheter or bronchoscope. Epinephrine or neosynephrine are also given because, by dilating the bronchial tree, they increase the degree of ventilation and facilitate the expulsion of secretions.

The type of antibiotic agent employed depends on the nature of the bacteria demonstrable in the sputum. For initial therapy, it is probably best to give aqueous penicillin in a dose of 250,000 units intramuscularly every 4 hours. When *H. influenzae* is present, the injection of 0.25-0.5 gm. of tetracycline or chloramphenicol intramuscularly every 6 hours is indicated. Difficulty may arise when *Staph. aureus* is the causative organism; in such cases, treatment should be started with penicillin, especially if the disease developed outside the hospital. It is imperative that the strain isolated from the sputum be examined promptly for sensitivity to various antibiotics and that the drug to which it is most susceptible be substituted for the penicillin as quickly as possible. Administration of the anti-microbial agents should be continued for 10 to 12 days.

Bronchiectasis

Bronchiectasis is a common progressive disease characterized by chronic infection and dilatation of the smaller bronchi and bronchioles. The mechanisms responsible for its development are (1) congenital abnormalities producing *persistent obstruction or ectasia,* (2) *acquired* bronchostenosis, of greatest importance in the pathogenesis of tuberculous bronchiectasis, (3) chronic bacterial infection of the bronchial wall, (4) pneumonia and its sequel pulmonary fibrosis, and (5) atelectasis, thought by many investigators to be present very commonly, if not in every case. The factors which are involved in producing chronicity are (1) destruction of the integrity of the bronchial wall by inflammatory reaction and (2) the normal stresses and strains of respiration which tend to dilate the bronchial tree, especially if there is obstruction to the outflow of air. Although

Because of the great fatigue, the ability to cough is diminished and secretions accumulate in the lungs to an even greater degree. Asphyxial depression of the vital centers in the medulla leads to arreflexia, disappearance of the corneal reflexes, dilatation of the pupils, twitching of muscles, depression of respiration, and finally shock. At this time, the cough disappears completely, accumulated secretions embarrass ventilation even more intensely, and death occurs. The disease may run its entire course, from onset to a fatal termination, in from 12 hours to 3 or 4 days.

The diagnosis of acute bronchitis superimposed on chronic pulmonary disease is based on the clinical findings and course described above. The conditions with which it is most often confused are left ventricular failure, with or without myocardial infarction, and pneumonia. Bacteriologic studies must be carried out immediately in order to determine the organisms responsible for the disease so that chemotherapy can be properly selected. Mixed infections are common. *H. influenzae* and the pneumococcus are present most frequently.

To be successful, treatment of this type of bronchitis must be directed along 3 main lines: (1) Relief of hypoxia, (2) increase of ventilatory adequacy, and (3) eradication of the organisms responsible for the infection.

Oxygen must be administered to all patients because some degree of hypoxia is always present. Individuals who have had chronic pulmonary disease for a long time often develop coma and stop breathing because the anoxia which has become the main stimulus to respiration is removed. For this reason, oxygen should not be given at first at a rate greater than 2 liters per minute; some cases will not tolerate more than 0 5 liter per minute.

Secretions which have accumulated in the bronchial tree must be removed. This is accomplished by encouraging the patient to cough, administering expectorants, instituting postural drainage, and, in some instances, aspirating the

bronchi by means of a rubber catheter or bronchoscope. Epinephrine or neosynephrine are also given because, by dilating the bronchial tree, they increase the degree of ventilation and facilitate the expulsion of secretions.

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bronchiectasis is usually an irreversible disease, it may, in some instances, disappear completely if properly treated in the very early stage. The disease may progress rapidly to an irreversible state as illustrated in one patient in whom this developed 7 weeks after a bout of pneumonia.

Despite the fact that many patients with bronchiectasis do not develop symptoms until adult life, the disease has its inception most frequently in childhood. The situations which predispose to its development are acute and chronic sinusitis, repeated infections of the upper respiratory tract, foreign bodies producing obstruction and atelectasis, tuberculosis, and measles and pertussis both of which are always accompanied by panbronchitis and are frequently complicated by bacterial pneumonia.

The most common symptom of bronchiectasis is cough; this is present in many patients for 10 years or more and in 50 per cent for at least 5 years before medical advice is sought. The amount of sputum and its characteristics are variable. In some cases, it is foul-smelling and produced in the largest quantity in the morning shortly after rising from sleep, as much as 2 cupsful per day may be expectorated. In other instances, sputum is absent or scant and does not have a distinctive odor. Hemoptysis occurs in 60 per cent of patients with bronchiectasis. It may consist only of minor streaking or of gross hemorrhage and is not related to the productiveness of the cough. In "dry bronchiectasis", repeated blood-spitting is common despite the absence of sputum. Clubbing of the fingers is present in 20 to 30 per cent of patients. Fever is not a striking feature unless the pulmonary lesion exacerbates or superimposed pneumonia appears.

There is some disagreement concerning the areas of the lung in which bronchiectasis is most frequently present. In one study of 200 patients, 51 per cent had bilateral basilar involvement; in 20 per cent the left and in 10 per cent the right lower lobe was affected. In 9 per cent, the disease was

present in both the right middle and lower lobes. In another investigation, the infection was unilateral in 53 per cent and bilateral in 47 per cent; lower lobes were found to be involved 3 times more frequently than upper ones, and the process was diffuse in 25 per cent. Bronchiectasis of the upper lobes is most frequently associated with tuberculosis. In general, it may be said that the lower portions of the lungs are involved more often than the upper ones, and that the disease is often bilateral and not rarely diffuse.

Although bronchiectasis usually starts in a single pulmonary segment, it may spread in some cases to involve several lobes of the lungs. As the lesion progresses, it is followed by marked fibrosis which finally results in complete occlusion of the bronchial system—bronchiolitis fibrosa obliterans. Patients with bronchiectasis are highly susceptible to repeated episodes of bacterial infection of the involved area of the lung Pulmonary abscess and empyema may occur. Among the other complications are brain abscess, amyloid disease, and arthritis of the rheumatoid type. Because of progressive fibrosis, cor pulmonale and right-sided heart failure develop in long-standing cases.

A variety of bacteria may be isolated from the sputum. Those present most often are the beta-hemolytic streptococcus, pneumococcus, *H. influenzae*, *Staph. aureus*, and the Friedlander bacillus. In some cases, the flora is relatively simple and is made up of only one or two organisms; in others, four or five different infectious agents are detected.

The presence of bronchiectasis should be suspected in patients with chronic productive cough and low grade fever. A history of repeated episodes of pneumonia or hemoptysis heightens the likelihood of the disease. Physical examination of the chest is unrevealing in most cases, although fine and coarse rales may be noted over the involved portion of the lung in some instances. X-ray of the chest may also not be helpful, especially in children in the early stage of the infection, the lungs frequently appear normal on routine

films or show, at most, slight infiltration or increased bronchovascular markings in the affected area. Bronchograms are indicated when the possibility of bronchiectasis is considered.

The treatment of bronchiectasis varies with the duration and extent of the disease and with the age and general condition of the patient. In its early stages, it may be cured purely by "medical" therapy; not all clinicians agree with this opinion, however, because they consider all phases irreversible. In patients who are young, in whom the changes demonstrable by bronchography are minimal, and who show little or no constitutional reaction, the administration of antibiotic agents selected on the basis of the organisms isolated from the sputum, re-expansion of atelectatic areas, the use of bronchodilators, and postural drainage may produce cure in some, but not all, instances. In cases with severe bronchiectasis accompanied by productive cough, hemoptysis and fever, lobectomy is indicated. This is carried out with the greatest degree of success in young individuals since the operative risk, especially in children, is very small. In people over the age of 40 years, the dangers associated with this operation make surgical therapy less useful. The contraindications to lobectomy are (1) the presence of active infection or other disease of the lungs, (2) decreased pulmonary reserve, (3) limited cardiovascular capacity, and (4) diffuse bronchiectasis. It has been said that patients should not be subjected to resection of the involved area if there is "too little or too much disease." In individuals who cannot be lobectomized, "medical" treatment as described above should be undertaken. When antibiotics are given, they should be administered in large doses for 2 to 3 weeks. If bronchiectasis is the result of tuberculosis, therapy is the same as for other forms of this disease (see below). Lobectomy may be carried out in some cases after the tuberculous process has been arrested. The use of antimicrobial agents for the prevention of secondary pneumonia

in patients with bronchiectasis is of questionable value and potentially dangerous because some of the organisms which invade the lungs during prophylaxis may be very difficult to eradicate.

Pertussis

Whooping cough is a common disease which affects about 85 per cent of all unimmunized individuals. The causative agent is *Hemophilus pertussis*, a short or ovoid gram-negative, non-motile, bacillus which is not pleomorphic, a feature which distinguishes it from *H. influenzae*. The disease is worldwide in distribution and may be either endemic or epidemic. The seasonal incidence varies in different geographic areas, being common in some places in the winter, and in others in the late summer or during autumn. Approximately 40 per cent of cases occur in the first two years of life. About 50 per cent of all children have had whooping cough before they reach the age of 5, 75 per cent have had it by the time they are 17 years old.

Pertussis is highly contagious and spreads by way of the respiratory tract. Transmission by fomites is very rare. The disease is most infectious during the catarrhal stage. Healthy carriers play no role in dissemination; mild or missed cases are of great importance. The duration of communicability is about 4 to 6 weeks.

The incubation period of pertussis averages 12 to 15 days, it may rarely be as long as 20 days. The first clinical manifestations are nonspecific in character and are usually mistaken for a viral infection of the upper respiratory tract. There is slight nasal discharge, conjunctivitis, and mild cough without fever. These symptoms of the *catarrhal stage* last for about 7 to 14 days.

The *paroxysmal phase* follows and is characterized by paroxysms of coughing provoked by even slight stimuli and ending in a loud, crowing inspiratory noise (the whoop), the expulsion of varying quantities of thick, mucoid sputum

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disease. The "convalescent" phase starts when all symptoms disappear; with modern treatment this stage is difficult if not impossible to recognize and define.

The peripheral white blood count is, as a rule, elevated in pertussis, there is a relative as well as absolute increase in the number of lymphocytes The total count may be over 100,000 per mm^3, and lymphocytes may constitute 90 or more per cent of the cells. All of the lymphocytes are mature. This distinguishes the blood picture from that of acute leukemia but not from acute lymphocytosis. Blood cultures are sterile. Serum electrolyte changes may be detectable in patients who have severe vomiting. Cultures of the nasopharynx reveal *H. pertussis*, the incidence of positive isolations varying with the stage of the disease (see below). X-ray study of the lungs in the uncomplicated case usually reveals only hilar lymphadenopathy and increase in density of the bronchovascular markings

One of the commonest complications of pertussis is bronchopneumonia, this occurs in from 1 to 10 per cent of cases. The organisms most frequently involved are the beta-hemolytic *Streptococcus, D. pneumoniae, Staph aureus, H. influenzae*, and *H. pertussis*. When pneumonitis appears during the course of chemotherapy, the bacteria most often responsible are *E. coli, Proteus* strains, *A. aerogenes*, or *Ps. aeruginosa*. Another pulmonary complication of whooping cough is atelectasis; although small areas of collapse are an almost constant finding in this infection, major portions or even a whole lung may be involved. Pneumothorax occurs rarely. Bronchiectasis may develop, especially if a bacterial pneumonia supervenes, this is said to be present in most fatal cases.

The severe coughing of pertussis may lead to several complications Hemorrhage may appear in the anterior chamber of the eye or in the subscleral, retinal, or subretinal areas. Detachment of the retina and blindness develop in a rare case. Prolapse of the rectum and inguinal and umbilical

from the respiratory tract, and vomiting. Episodes of cough may be as few as 1 or 2 or as many as 40 to 50 per day, and occur with greatest frequency at night. Children under the age of 6 months frequently do not whoop. The mere presence of a whoop is in itself not diagnostic of pertussis because other infections of the bronchopulmonary tree may occasionally produce the same symptom. In a few cases, the cough is preceded by an aura which may consist of discomfort in the nose or throat, yawning, or sneezing.

Significant fever does not occur in the paroxysmal phase of pertussis unless dehydration, secondary infection, encephalopathy, or other complications are present. Vomiting frequently follows coughing episodes but is not a specific manifestation of the disease. Soreness over the trachea and main bronchi are common. Intense paroxysms produce a sensation of strangling, particularly in adults. Repeated cough may be responsible for abdominal pain. Spasm or ulcer or, more rarely, edema of the glottis sometimes develop. In instances in which severe vomiting and inability to retain food have been persistent, serious degrees of starvation may be present, and tetany may appear. Although hemoptysis, epistaxis, purpura of the skin, and subconjunctival or intestinal hemorrhages may occur, these do not have a bad prognostic significance.

Physical examination in cases of pertussis is often entirely normal. There may be redness and injection of the blood vessels of the nose and pharynx. Fine, crackling, inspiratory or "sticky" rales which change with coughing are sometimes, but not always, present and not specific for the disease. Because of enlargement of the hilar lymph nodes, D'Espine's sign is frequently elicited. There are ulcers of the frenum of the tongue in about 20 per cent of children who have lower central incisor teeth. The paroxysmal stage of pertussis usually lasts for 1 to 6 weeks. When coughing persists

oxysms, the organisms can be isolated from about 75 per cent of patients, in the second week from 60 per cent, in the third week from 45 per cent, and by the fifth week from less than 10 per cent. Serologic studies are of little value in diagnosis; skin testing for immunity is of doubtful value.

Although all of the antimicrobial agents have been employed in the treatment of pertussis, there is no evidence that they are strikingly beneficial. Aureomycin (chlortetracycline), chloramphenicol, Terramycin (oxytetracycline) and erythromycin have been used, but the results obtained in controlled studies indicate little or no effect on the primary disease or the incidence of complications. Secondary bacterial infections occurring during chemotherapy are often more difficult to manage than those which appear when no drug is given, because the organisms involved are, in many instances, not sensitive to the available antibiotics. Serum therapy is thought by some to be effective in beneficially altering the course of whooping cough; controlled studies, however, have not indicated a striking therapeutic effect.

The most successful methods of management of pertussis are entirely non-specific. Most important in the program of therapy is repair of water and salt loss which follows the severe and frequent vomiting which may be present. Failure to retain food is combatted by prompt re-feeding. With proper care, whooping cough patients will maintain or gain weight.

Early detection and treatment of complications is one of the most important factors in the reduction of mortality in all cases. When gross atelectasis occurs, correction by tracheal catheter suction or bronchoscopy may be lifesaving. Little can be done to influence the course or outcome of gross cerebral hemorrhage or encephalopathy. The prevention and correction of metabolic disturbances and prompt

hernias have been noted. Otitis media is observed in about 10 per cent of cases; the organisms most frequently involved are the beta-hemolytic *Streptococcus* and *Staph. aureus*, although *H. pertussis* is sometimes responsible.

Nervous system manifestations are not rare in pertussis. The commonest symptom is convulsions; these are often due to the sudden appearance of fever accompanying a secondary bacterial infection. The other causes of seizures are encephalopathy (1 to 14 per cent of cases), multiple petechial or gross hemorrhages of the brain, and cerebral anoxia due to the combined effect of anoxic anoxia and venous stasis in the brain due to severe and persistent coughing. The encephalopathy is accompanied by an increase in the protein and cell content of the spinal fluid, and is responsible for a wide variety of neurological signs including coma, convulsions, paralyses, and other localizing signs. Death may occur. Residua are relatively common.

The diagnosis of pertussis is made on the basis of a history of paroxysms of typical coughing and whooping, which appear after a short period of an undefined upper respiratory tract infection. It must be stressed, however, that babies under the age of 6 months usually have only paroxysmal coughing, without whoop. Laboratory studies help to confirm the diagnosis. An increased white blood count with relative lymphocytosis is characteristic; the lymphocyte count must, however, be evaluated in relation to the age of the patient. X-ray examination of the lungs is not diagnostic.

Isolation of *H. pertussis* from the respiratory tract establishes the diagnosis; unfortunately this is not possible in many instances. Using cough plates and nasopharyngeal swabs, positive cultures can be obtained in 90 per cent of cases in the catarrhal stage; the disease is, however, rarely seen by the physician in this phase. The incidence of positive cultures is lower after coughing appears, and decreases with the duration of symptoms. In the first week of par-

which may be of help in etiologic differentiation in special instances.

Mode of Onset: Pneumonia may appear very suddenly in perfectly well individuals or follow manifestations of upper respiratory disease which have been present for as long as a week or more. It may also occur as a complication of other conditions such as pertussis, measles, rheumatic fever, typhus, cardiac failure, trichinosis, or after exposure to birds (psittacosis) or various chemicals (gases, kerosene, oils, etc.).

Fever: Elevated temperature is present in practically all cases of pneumonitis. The fever may be sustained at high or low levels, remittent, or intermittent, but is not sufficiently characteristic to indicate specific etiology. Chills are common in some types of pneumonia (pneumococcal, streptococcal) and absent in others. Their presence is not always directly related to the type or severity of the infection.

Cough and Sputum: Cough is the outstanding symptom of pneumonia. It may be mild or so severe that it produces major discomfort. It must be stressed that cough is absent in some cases of pneumonitis. The writer has studied a number of patients who had fever and significant pulmonary infiltration on x-ray examination but did not cough; no bacteria were recovered, and it was presumed that the disease was due to an unidentified virus. The presence of a cough does not necessarily indicate parenchymal involvement of the lung since it is common with infections of the pharynx, larynx, and trachea.

The production of sputum is not diagnostic of specific types of pneumonia in individual patients. In general, sputum is practically always present with bacterial infection of the lungs and absent when viruses are the causative agents. However, "atypical viral pneumonia" may be accompanied, from its inception, by a productive cough. The gross appearance of the sputum may be characteristic for certain kinds of pneumonia. Thus, light blood streaking or

treatment of secondary bacterial infections are, in the main, responsible for the present very low death rate in this disease.

Pertussis vaccine prevents the development of the disease in 90 per cent or more of the patients who receive it. Immunization should be started at the age of 2 to 3 months. "Booster" doses are given at one year of age and just before a child goes to school. The use of combined tetanus-diphtheria-pertussis (DPT) vaccine produces better results than when each agent is given alone. Severe encephalopathy resulting in death or survival with severe neurologic residua is a rare complication of immunization against whooping cough.

In children who have been exposed to a case of pertussis but have not been actively immunized, passive protection may be produced for 3 to 4 weeks by the administration of 20 to 30 ml. of human hyperimmune serum or 2 to 3 ml. of "immune" gamma globulin. Such prophylaxis is effective in 75 to 85 per cent of cases.

Pneumonia—General Features

Pneumonia is a common disease. It occurs most often in patients less than 3 years and over 40 years old, although it may appear at any age. Bacteria, viruses, rickettsiae, protozoa, worms, and spirochetes may be the responsible agents. In many instances, the pulmonary process appears as an isolated disease. In some, however, it is a regular feature or complication of some other infection.

The clinical features of pneumonia are, with some exceptions, qualitatively the same regardless of the nature of the causative agent. General manifestations of infection (fever, chills, malaise, headache, etc.) and the signs and symptoms of disease of the lungs (cough, dyspnea, sputum, hemoptysis, chest pain) constitute the syndrome of pneumonitis. There are, however, some quantitative differences

decreased movement on the involved side with respiration; in diffuse bronchopneumonia, differences in motility are not apparent. The earliest sign of pneumonitis is suppression of breath sounds over the affected area. It is very important that auscultation be carried out in the axillae because the decrease in intensity of breathing is frequently first detected here. The signs may not progress beyond this point if therapy is instituted. If treatment is not given, rales of varying quality usually appear. In pneumococcal pneumonia and other infections in which consolidation of the lung develops, dullness to percussion, bronchial breathing, increased tacticle and vocal fremitus, whispered pectoriloquy, and egophony become detectable in 24 to 48 hours. If antibiotics are administered early, the signs of consolidation never appear. In interstitial pneumonitis, the breath sounds have an asthmatic character; wheezing on expiration is striking.

X-ray Examination: Roentgenographic study is the most important method of establishing the presence of pulmonary involvement. It must be stressed, however, that etiologic diagnosis cannot be made on the basis of the x-ray appearance of the lungs. Certain features may be suggestive but there are many exceptions even to these. Thus, while lobar consolidation is consistent with pneumococcal infection, it may be present when other bacteria or viruses are the causative agents. Enlargement of the hilar lymph nodes and increased density of the bronchial markings radiating toward the base of the lungs is observed in many cases of "atypical viral pneumonia"; these findings are also present in pertussis. Sagging of the interlobar fissure occurs with invasion by the Friedlander bacillus, it is absent in some cases. Lateral views of the chest should be obtained when an anterior-posterior film reveals no evidence of disease because infiltration may develop first in the retrocardiac portions of the lungs, especially with "virus" pneumonia. The presence of lesions such as bronchiectasis or carcinoma of

a brown color is common with pneumococcal pneumonia; this is not always the case, however. Thick, gelatinous, "prune-juice" sputum is frequent when the Friedlander bacillus invades the pulmonary parenchyma, but these features are entirely absent in some cases. The sputum of staphylococcal infection is "purulent" but the same feature may be observed when other organisms are involved. Microscopic study of the sputum is often of help in differentiating viral from bacterial disease; the presence of a large number of neutrophiles suggests the latter, while lymphocytes predominate in the former. Eosinophiles are present when manifestations result from a reaction of hypersensitivity.

Pleuritic Pain and Pleural Effusion: Pleurisy is more common in some types of pulmonary infection than in others. Pneumococcal pneumonia frequently starts with pleuritic pain; this is not true in every case, however. While chest pain is uncommon in most viral pneumonitides, it may be striking in an occasional case. Discomfort in the substernal area and over the trachea and bronchi is more frequent with viral than with bacterial disease. Pleural effusion is common in some forms of pneumonia. It occurs in most cases due to the beta-hemolytic streptococcus, but is also observed when the pneumococcus, staphylococcus, and other bacteria are responsible; it is noted only rarely with virus infections. The fluid may contain organisms or be sterile. A preponderance of polymorphonuclear leucocytes and reduction in sugar content are consistent with the presence of bacteria. Blood may be present; its detection is of little help in indicating specific etiology.

Physical Examination: Tachypnea, dilatation of the alae nasi, labored or grunting respiration, retraction of the ribs and lower end of the sternum in children, and cyanosis are present in pneumonia without relation to specific etiology. They are often significant in indicating the severity of the pulmonary process. Examination of the chest usually reveals

BACTERIAL PNEUMONIA

Pneumococcal Pneumonia

Pneumococcal pneumonia often starts without a preceding respiratory tract infection, although a "cold" may have been present for a few days prior to the onset. The earliest manifestations are fever, shaking chills, pleuritic pain and cough productive of sputum which may be blood streaked or brown in color and contains polymorphonuclear leucocytosis. Physical examination at this time usually reveals diminution of breath sounds, dullness to percussion over the involved lobe, and limitation of motion of the affected side. In children, the pneumococcus frequently produces broncho- instead of lobar pneumonia. X-ray shows infiltration usually in one of the lower lobes. If treatment is not instituted, the process progresses until complete consolidation with its characteristic physical and roentgenographic findings appears.

The antibiotic of choice for the therapy of pneumococcal pneumonia is penicillin. The intramuscular injection of 600,000 units once daily until the temperature has been normal for 5 days cures the disease and prevents complications in most cases. Aureomycin (chlortetracycline), Achromycin or Tetracyn (tetracycline) and erythromycin are also effective. These agents are administered by mouth in a dose of 0.25 gm. every 6 hours for the same period as penicillin. If therapy has been delayed or complications are present, it is best to give aqueous penicillin, 500,000 units intramuscularly every 4 to 6 hours. No strains of pneumococci are resistant to any of the drugs mentioned.

The incidence and prevalence of pneumococcal pneumonia have not been decreased by the use of potent antimicrobial agents. Some of its features have, however, been altered. Thus, higher serologic types of the organism are more frequently involved, more older individuals are

the lung which predispose to acute pulmonary infections may be revealed by roentgenographic examination.

Laboratory Findings: Although bacterial pneumonias are usually accompanied by leucocytosis, the white blood count may be normal or, in severe and extensive infections, depressed. The same is true for the number of polymorphonuclear leucocytes. In virus and other diseases of the lung, *leukopenia or a normal white blood count, often with lymphocytosis,* is the most common finding but leucocytosis may also be present. It is not possible, therefore, to differentiate the etiologic type of a pneumonitis on the basis of blood counts.

The most important laboratory studies in pneumonia are concerned with the identification of the causative agent. Sputum, if available, must always be cultured promptly on appropriate media. If cough is unproductive, a culture of pharyngeal secretions often reveals the responsible bacteria. In viral infections, it is not practical to attempt to isolate the organisms, serologic tests are of greatest diagnostic value in such cases (Chapter I). Blood cultures should be made in every case of pneumonitis because bacteremia confirms the causal relationship of the bacteria recovered from the sputum and has prognostic importance.

"Unresolved" Pneumonia: The bacterial pneumonias clear *rapidly as a rule. Infiltration of the lung may persist,* however, for weeks or even months when various viruses are the cause of the infection Persistence of the pulmonary lesion after the acute phase of the disease is over raises the possibility of the presence of a complicating factor. The following causes of "unresolved pneumonia" must be ruled out: (1) tuberculosis, (2) bronchiogenic carcinoma, (3) atelectasis, (4) lung abscess, and (5) serous or purulent pleural effusion which is usually located in the interlobar area.

Complete immunity is not produced in every case but the risk of complications and death is reduced in those in whom pneumonia occurs.

Staphylococcal Pneumonia

Pneumonia due to *Staph. aureus* is rarely, if ever, a primary disease. It is usually secondary to staphylococcal infection elsewhere in the body, bacteremia, or viral infection of the lungs (influenza for example), or occurs as a superinfection during antibiotic therapy for another disease.

There are very few features which distinguish staphylococcal from other types of bacterial bronchopneumonia. The onset may be insidious or similar to that of pneumococcal pneumonia. The sputum is purulent and contains large numbers of polymorphonuclear leucocytes and organisms. Anatomically the disease is characterized by multiple small abscesses which often coalesce to form large ones. Because of their subpleural location and the rapidity with which they rupture, empyema is a frequent complication. Air usually escapes into the chest cavity and produces pyopneumothorax. This is pathognomic of staphylococcal pneumonia and is observed most often in children.

The course of untreated staphylococcal pneumonia is often prolonged, characterized by alternating episodes of high-grade fever and low temperature, and frequently terminates fatally. In cases which recover, extensive pulmonary fibrosis may be present. Bacteremia is frequent. Among the complications are brain abscesses, meningitis, empyema, acute bacterial endocarditis, suppurative arthritis, and metastatic infection of any organ.

A history of a predisposing situation, the presence of bronchopneumonia, purulent sputum, and pyopneumothorax are highly suggestive of staphylococcal infection of the lungs. The diagnosis is confirmed by isolation of coagulase-positive, hemolytic, *Staph. aureus* from the sputum or blood, or both. Care must be exercised in attributing causal sig-

affected, complications are less frequent, and the fatality rate has been reduced. It must be stressed that complications and death (5 per cent) still occur in some cases. The factors of importance in prognosis prior to the antibiotic era are also *significant in treated cases, although to a lesser* degree. These are

(1) *Age*—older patients and babies are more likely to experience difficulty than patients aged 10 to 30 years.
(2) *Number of lobes involved*—the more extensive the pulmonary involvement, the greater the risk of complications or a fatal outcome.
(3) *Presence of other disease*—patients with debilitating disorders such as chronic liver disease, cardiac decompensation, blood dyscrasias, etc., do not respond optimally to chemotherapy.
(4) *Bacteremia*—the presence of pneumococci in the blood increases the dangers of this disease.
(5) *Time of treatment*—the longer the period which elapses between the onset of pneumonia and the initiation of therapy, the poorer the outlook for uncomplicated recovery.
(6) *Serologic type of the organism*—infections due to types III and VIII are probably more serious than those due to other serotypes even in patients treated with antimicrobial agents.

Pneumococcal pneumonia may be prevented by the administration of type-specific polysaccharide. Protection is not general but limited to the serologic types included in the vaccine. Because of the ease with which this disease can be treated, immunization has very little practical application except in special situations. Elderly people living in large numbers in various institutions are very susceptible to this disease which may become widespread; it is probably worthwhile to protect them against pneumococcal infection. The vaccine contains the polysaccharides of types 1, 2, and 3.

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nificance to staphylococci recovered from the respiratory tract because 20 to 60 per cent of normal people harbor these organisms in their nose or throat. There must be clinical and roentgenographic evidence of pulmonary involvement to support the diagnosis.

The treatment of staphylococcal pneumonia may be very difficult. Determination of the sensitivity of the organisms to various antibiotics as quickly as possible is imperative. If the disease has been contracted outside the hospital, there is an 85 per cent chance that the bacteria are sensitive to penicillin; if it occurs in a hospitalized patient, susceptibility to antimicrobial agents is unpredictable. Although staphylococcal pneumonia demands immediate therapy, sputum and blood must be obtained for bacteriologic study before antibiotics are given. The initial treatment for the disease acquired outside the hospital is 500,000 units of crystalline benzyl penicillin G every 4 to 6 hours. When the pneumonia develops in the hospital, it is best to administer chloramphenicol plus erythromycin, 0 5 gm. of each, orally or parenterally every 6 hours. As soon as the organisms have been isolated, they must be examined for sensitivity to penicillin, the tetracycline compounds, chloramphenicol, novobiocin (Cathomycin), streptomycin, bacitracin, and neomycin. If the drugs being used are found to be ineffective *in vitro*, the ones to which the staphylococci have been found most susceptible must be substituted. Chemotherapy should be continued for a minimum of 2 weeks; it may need to be given longer if complications develop. Sputum cultures should be obtained frequently during the course of treatment in order to determine whether other organisms have invaded, or whether the staphylococci have become insensitive to the antimicrobial agents which the patient is receiving. The risk of death from staphylococcal pneumonia is high even when antibiotics are administered; about 50 per cent of cases still terminate fatally.

H. Influenzae Pneumonia

H. influenzae is a common cause of primary pneumonia in children. It rarely produces pulmonary infection in adults unless another respiratory disease such as measles, "viral" pneumonia, or influenza is present.

The clinical and laboratory features of influenzal pneumonia are not diagnostic. Pneumonitis occurring in a young child, following upper respiratory manifestations, measles, pertussis, or the administration of penicillin for another infection is highly suggestive. Physical examination and x-ray study of the lungs do not reveal the etiology, since the findings are the same as those in other types of bronchopneumonia. The diagnosis is made by isolation of *H. influenzae* from the respiratory tract or blood, or both.

The drugs of greatest value in the therapy of influenzal pneumonia are the tetracyclines and chloramphenicol. Achromycin (tetracycline) 50 to 75 mg. per Kg. per day divided into 4 equal doses given at 6 hourly intervals, produces cure in most cases. Chloramphenicol in the same quantity is also highly effective, some physicians prefer to give this drug together with 0.1 gm. of sulfadiazine per lb. of body weight per day, the initial dose being one-half of the daily requirement. Streptomycin (50 mg. per Kg. per day in divided doses) has also been used in combination with sulfadiazine or sulfisoxazole (Gantrisin). Treatment should be continued in all instances for at least 10 days.

Streptococcal Pneumonia

Infection of the lungs by the beta-hemolytic streptococcus is uncommon. It is practically always secondary to streptococcal pharyngitis, pertussis, measles, or pulmonary diseases due to viruses.

The onset of streptococcal pneumonia is usually sudden. Fever, shaking chills, restlessness, cough, dyspnea, cherry-

red cyanosis, and blood-streaked sputum are the outstanding manifestations. Respiratory symptoms are severe because of the diffuse interstitial location of the disease. The physical and x-ray findings indicate an extensive bronchopneumonia. Empyema is a frequent and early feature; it appears in 40 to 60 per cent of patients within 48 to 72 hours after onset. The pleural fluid is serous or serosanguinous and contains many organisms and a reduced content of sugar. The other complications of streptococcal pneumonia result mainly from the bacteremia which often accompanies it; they are acute endocarditis, pyogenic arthritis and meningitis.

The possibility of streptococcal pneumonia is usually suspected on the basis of the mode of onset of the disease, the severe clinical manifestations, and the early appearance of pleural effusion; it is confirmed by the isolation of beta-hemolytic streptococci (group A) from the sputum, blood or pleural effusion.

The treatment of choice for pulmonary infection due to group A beta-hemolytic streptococci is penicillin. The intramuscular injection of 600,000 units of the procaine ester of this drug once daily for 10 to 12 days usually produces rapid cure, if complications are not present. Some clinicians prefer to give 250,000 to 500,000 units of aqueous penicillin intramuscularly every 6 hours. If pleural effusion appears, 50,000 to 100,000 units of soluble penicillin should be injected into the pleural space at least once, in addition. In patients sensitive to penicillin, the administration of 0.25-0.5 gm. of erythromycin orally every 6 hours is recommended.

Friedlander Bacillus (K. pneumoniae) Pneumonia

Prior to the chemotherapeutic era about one per cent of all pneumonias were due to the Friedlander bacillus. There have been some recent suggestions that the number of infections due to this organism is increasing.

The onset of Friedlander bacillus pneumonia is often very abrupt and may be difficult to differentiate from pneumococcal infection because shaking chills, high fever, pleuritic pain, and cough productive of thick and sometimes blood-tinged sputum are common. The tenacious, prune-juice sputum which is said to be characteristic is not observed very often; its absence does not rule out the disease. The upper lobes of the lungs are involved more frequently than the lower ones. Sagging of the interlobar fissure is a very helpful x-ray finding, when present.

The course of the disease is frequently brief and catastrophic. In the days before chemotherapy, 75 to 99 per cent of the patients died. Tissue destruction is rapid and extensive; the alveolar walls are destroyed, and the whole lung parenchyma is involved in an acute and severe necrotizing process. Cavitation and a tendency to organization and fibrosis are common. Friedlander bacillus pneumonia may become chronic in a small number of patients even when antibiotic therapy is administered. In these cases, multiple cavities, advancing bronchiectasis, and gradual scarring of the lung develop over a period of weeks or months and produce a picture which is difficult to differentiate from far-advanced pulmonary tuberculosis. These changes may appear immediately after the acute phase of the pneumonia in some instances.

Most Friedlander bacillus infections occur during the fourth, fifth, and sixth decades of life. In children, they are observed most frequently during the first 2 years of life. Chronic disorders of various types predispose to invasion of the lung by *K. pneumoniae*. Many patients are alcoholics and have a varying degree of hepatic insufficiency.

Treatment for Friedlander bacillus pneumonia should be initiated as early as possible. Delay makes the prognosis poor regardless of the antibacterial effectiveness of the drugs employed. Penicillin is ineffective in this type of disease. Combined antibiotic therapy is best. Although the

organism is sensitive to streptomycin, the use of this agent alone may lead to the appearance of an insensitive strain. Streptomycin (0.5 gm. intramuscularly every 6 hours) plus sulfadiazine in full doses have proved successful in some cases. The combination of chloramphenicol and streptomycin (0.5 gm. of each intramuscularly every 6 hours) is more effective. It has been suggested that chloramphenicol, chlortetracycline (Aureomycin) and oxytetracycline (Terramycin) given together produce even better results. The writer prefers not to use 3 antibiotics at one time because of the increased risk of untoward effects. X-ray study of the *lungs should be carried out frequently to determine whether* or not progression with cavitation is occurring despite an apparently satisfactory clinical response. With the best *therapy available, the fatality rate in K. pneumoniae* infection of the lungs is still 20 to 25 per cent. Bacteremia is not an important prognostic factor. The management of chronic *Friedlander bacillus pneumonia is essentially* the same as that for fibrocavernous tuberculosis. If, after an adequate trial of chemotherapy, cavity closure does not occur, segmental resection, lobectomy, or pneumonectomy, depending on the extent of the disease, is indicated.

Pertussis Pneumonia

Pneumonia occurring in the course of whooping cough is usually due to *H. influenzae,* the pneumococcus, beta-hemolytic streptococcus, or *Staph. aureus.* It may also be produced by *H. pertussis,* however. Infection of the pulmonary parenchyma by this organism produces no distinguishing clinical, laboratory or roentgenographic features. The diagnosis is made by demonstrating the presence of *H. pertussis* and the absence of other pathogenic bacteria. An elevated white blood count with a marked increase in lymphocytes *is the rule. There is no specific therapy (see above).*

Salmonella Pneumonia

The two types of salmonellosis in which pneumonia may occur are typhoid fever and S. *choleraesuis* infection. The typhoid bacillus may produce either lobar or diffuse involvement of the lungs; pleural effusion is present rarely. Pneumonitis due to S. *choleraesuis* is a complication of the enteric or septicemic types of disease produced by this organism; metastatic infection is also present in other locations in some cases (Chapter IX). Pneumonitis produced by *Salmonellae* has no distinguishing features. The pulmonary lesions are usually bilateral and diffuse. The diagnosis is made by isolation of the causative agents from the blood, sputum, or stool. Treatment is the same as for the primary disease of which the pulmonary involvement is a complication (Chapter IX).

Tularemic Pneumonia

Pneumonia develops in from 10 to 25 per cent of cases of ulceroglandular or typhoidal tularemia. It is present as an isolated disease in 35 per cent of patients infected with *Pasteurella tularensis;* the diagnosis is usually not suspected in these instances The possibility of tularemic pneumonitis should be suspected in individuals living in an area where this disease is endemic when they present themselves with an acute and severe pulmonary disease with fever and leucocytosis. Since the process progresses rapidly and is often fatal, it is very important that the diagnosis be established as rapidly as possible and therapy initiated promptly. The sputum and blood should be cultured in cysteine broth The treatment of tularemia is discussed in Chapter XV.

VIRUS PNEUMONIAS

Measles Virus Pneumonia

In addition to panbronchitis which is present in all cases of rubeola, about 50 per cent of patients have an interstitial

pneumonia probably due to the measles virus. Secondary infection of the lungs occurs much less commonly (approximately 2 per cent) and is usually produced by the beta-hemolytic streptococcus, *H. influenzae*, the pneumococcus, or *Staph. aureus*. It is often difficult to differentiate bacterial from viral pulmonary involvement in rubeola. The following criteria may be of help in pointing to the possibility of invasion of the lungs by bacteria: (1) Recurrence of fever and a change in the physical findings in the chest in a patient in whom the temperature has been coming down or in whom complete defervescence has taken place. (2) Appearance of leucocytosis with evidence of pneumonitis; encephalitis must be ruled out because elevation of the white blood count frequently accompanies this complication. There is no specific therapy for measles virus pneumonia.

Primary Varicella Pneumonia

Severe pneumonia may be produced by the virus of chicken pox. Viral involvement of the lungs occurs most frequently at the height of the skin eruption and is observed only in adults. The disease is more common than is suggested by the small number of cases reported in the medical literature. Some cases are mild and, although cough is prominent, other symptoms of pulmonary infection are minimal or absent, and physical examination of the chest reveals no abnormalities. More often, however, severe manifestations are present. The temperature is high, tachypnea is marked, dyspnea and cyanosis are striking, and the patient appears critically ill. The rash is hemorrhagic in most instances. Diffuse inspiratory rales, expiratory wheezing, and diminution in breath sounds in some or signs of consolidation in other cases are frequently detectable. Even with severe primary varicella pneumonitis, examination of the lungs may be totally unrevealing. X-ray study usually shows diffuse parenchymal infiltration of the lungs, the lesions having

a nodular appearance. The white blood count is often elevated, and there is a relative increase in neutrophiles. Cultures of the throat and sputum, when present, usually do not yield pathogenic bacteria. Although recovery is the rule, death occurs occasionally. The pulmonary infiltrate may not clear completely for many weeks. There is no specific therapy.

Some patients with chicken pox develop secondary bacterial pneumonia. This may be difficult to differentiate from disease produced by the virus of varicella; the detection of nodular pulmonary lesions by x-ray study may be helpful. If the pneumonitis is due to bacteria, it must be treated with the appropriate antibiotic agent.

Influenza

The influenza virus affects primarily the upper respiratory tract. However, the lungs may also be involved in some patients. Although this is more common when the disease is pandemic, it has also been noted in epidemic and sporadic cases. There are no features which distinguish it from other kinds of viral pneumonitis. Secondary bacterial infections of the lungs also occur in influenza and are frequently due to *Staph. aureus*. There is no effective treatment for influenzal viral pneumonitis. When bacteria are responsible, therapy with appropriate antibiotic drugs must be undertaken.

Psittacosis—Ornithosis

Pneumonia due to the psittacine-ornithine group of viruses is not rare. It is very important, therefore, to attempt to elicit a history of contact with birds—pigeons and members of the parakeet or parrot families—in any case of "atypical virus pneumonia" because, with the exception of the epidemiologic background, it is impossible to distinguish psittacosis from other types of viral pneumonitis clinically. The manifestations of psittacine pneumonia are usually

severe; the disease may be quite mild, however. Intense, harassing, non-productive cough, a varying degree of fever, headache, retrobulbar pain exaggerated by movement of the eyes, and generalized bone and muscle aching are common. Physical examination of the chest may reveal no changes or only diminished breath sounds and a few rales; signs of consolidation appear in some cases. Dyspnea and cyanosis are striking with severe infection. Relative bradycardia is common. Roentgenographic study of the lungs frequently shows diffuse, mottled infiltration; with mild disease, only enlargement of the hilar nodes and increased bronchovascular markings may be detectable. The white blood count is normal or elevated; lymphocytosis is present in some instances. The course of psittacosis is variable; all of the signs and symptoms may persist for 2 weeks or longer. Complications are uncommon; exudative erythema multiforme (Stevens-Johnson disease) has been observed in a rare instance. Secondary bacterial infection of the lungs is rare. The majority of patients recover without specific therapy, but death occurs occasionally.

The diagnosis of psittacosis is suspected in patients with manifestations consistent with "viral pneumonia" who have had contact with birds. It is proved by demonstration of a significant increase in titer of complement fixing antibody for the virus when serums obtained in the acute phase of the disease and during convalescence are compared.

Psittacosis is treatable. This emphasizes the necessity of obtaining an adequate epidemiological history since this is the only basis on which a diagnosis can be made early in the disease. The drug of choice is tetracycline; it is administered in a dose of 0 25 gm. orally every 6 hours for 10 to 12 days. Despite clinical recovery, pulmonary infiltrates may persist for weeks or months and occasionally raise the question of tuberculosis or other causes of "unresolved pneumonia".

"Atypical Viral Pneumonia"

"Atypical viral pneumonia" is a syndrome and not a specific disease entity. It may be produced by a number of agents, some of which have been identified and others of which have not yet been isolated. The adenoviruses have recently been proved to be responsible for some cases of this disorder. In most instances, manifestations of an upper respiratory tract infection—cough, sore throat, coryza—are present for a varying period before pneumonitis develops. The clinical features of "atypical viral pneumonia" are quite variable. In some patients, fever is of low degree, cough is minimal, and examination of the chest reveals no abnormalities; x-ray of the lungs, however, shows infiltration. At the other extreme, are the cases in which the signs and symptoms are severe. High grade fever, intractable, harassing, non-productive cough, headache, intense malaise, retrobulbar pain, and even dyspnea, cyanosis, and pleuritic pain are present. Physical examination of the chest may be unrevealing even in such cases, although suppression of breath sounds, rales, and, in a few instances, signs of consolidation may be present; sterile pleural effusion occurs rarely. Dissociation between the physical and roentgenographic findings is characteristic of this kind of pneumonia. Thus, physical examination of the lungs may reveal very little when the x-ray shows diffuse infiltration, and vice versa. The white blood count and differential are usually normal. Occasionally, leukopenia with relative lymphocytosis or leucocytosis with an increased number of neutrophiles is present.

The diagnosis of "atypical viral pneumonia" is usually made clinically on the basis of the onset and course of the disease, and the x-ray picture of the lungs. It must be stressed that failure of a pneumonitis to respond to treatment with antibiotics does not prove that it is of viral etiology.

Serologic studies may be helpful. In some types of "atypical pneumonia" there is a significant increase in serum titer of cold agglutinins and agglutinating antibody for Streptococcus MG; 50 per cent of patients develop one of these antibodies. Both are detectable in some instances. Complement-fixation studies for adenoviruses should be carried out in every case.

Complications rarely appear in "atypical viral pneumonia". Secondary bacterial infections of the lungs are very uncommon. Pleuritis with friction rub, sterile pleural effusion, acute serofibrinous or "benign" pericarditis, and "aseptic" meningitis or meningoencephalitis have been described but are infrequent. Erythema multiforme exsudativum, especially the Stevens-Johnson syndrome, occurs occasionally and is responsible for prolonged and severe illness.

Whether or not the use of antibiotics is effective in the treatment of "atypical viral pneumonia" is still debated. There is no doubt that some cases respond very promptly to these drugs, and that others are totally unaffected. Variability in response is probably due to the fact that the disease is caused by different viruses, some of which are susceptible and others insensitive to the antimicrobial compounds; the adenoviruses, for example, are not affected by antibiotics. It is the writer's practice to withhold therapy in mild episodes of "atypical virus pneumonia", especially when fever is low and respiratory symptoms are minimal or moderate in intensity. The use of drugs in such instances probably exposes the patient to a risk of untoward effects greater than the benefits to be derived. When the temperature is high (103° or higher), cough severe, and pulmonary infiltration extensive, the administration of tetracycline, chlortetracycline (Aureomycin), oxytetracycline (Terramycin), or chloramphenicol is indicated. The usual dose of these drugs is 0.25 gm. given orally every 6 hours for 7 to 10 days. The course of the pneumonia is not altered by such treatment in some patients.

Viral Pneumonia of Childhood

One type of pneumonia which occurs in the neonatal period *is thought to be due to a virus. The disease usually* appears within 5 to 6 days after birth. There is frequently a history of respiratory tract infection in the mother. Clinical manifestations are often very severe, and x-ray examination of the lungs reveals diffuse infiltration. Death may occur. The causative agent has not been isolated or identified. It has been suggested that some cases are produced by distemper virus because antibodies to this organism are present in the serum of children who recover. Epithelial cells containing intracytoplasmic inclusion bodies are present in pharyngeal smears and are thought to be diagnostic of this type of infection.

Mycotic Infections of the Lungs

Pulmonary Moniliasis and Torulosis

Acute pulmonary infection due to Candida (Monilia) or Torula is uncommon. It rarely occurs as a primary disease but is usually secondary to other conditions such as lymphoma and leukemia. It is thought to be increasing in incidence as a result of superinfection of the lungs resulting from the use of antibiotic agents, particularly the so-called "broad spectrum" drugs. Diffuse pneumonia or lobular or lobar consolidation may be present. The physical and x-ray findings do not differentiate this type of pneumonitis from that due to other infectious agents. The sputum may have a "beery" odor.

The only method of establishing the diagnosis of pulmonary moniliasis or torulosis is by isolation of the organism from the sputum by culture on Saboraud's *medium or corn* meal agar. Great caution must be exercised in attaching etiologic significance to these organisms because they are present in the upper respiratory tract of many normal per-

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Coccidiomycosis

Coccidiomycosis is produced by the fungus, *Coccidiodes immitis*, the spores of which enter by way of the respiratory tract. The disease has been observed primarily in California, especially in the southern San Joaquin Valley. It has also occurred in Texas, New Mexico, Arizona, Nevada and Utah in the United States, and in Paraguay, Bolivia, Argentina, Venezuela, and Italy.

Coccidiomycosis may appear as an asymptomatic disease, as a respiratory syndrome resembling influenza or pneumonia, or as progressive disseminated process—coccidiodal granuloma. Asymptomatic infections are never recognized in the acute stage and are diagnosed only in retrospect on the basis of a positive skin test. The primary influenza- or pneumonia-like type is acute and accompanied by one or more of the following symptoms and signs: fatigue, general malaise, pleuritic pain, non-productive cough, minor hemoptysis, chills, fever, erythema nodosum, eosinophilia, and arthralgia. Abnormal physical findings may appear over the lungs. X-ray studies reveal various abnormalities. The earliest lesion varies from slight fuzzy thickening of the hilar shadow to light, veil-like infiltration, to consolidation which occupies a major portion of the lung fields. Nodular parenchymal opacities may be present. These are generally found in the mid-lung field; they are detected less often in the lower lobes and least frequently in the apical and subapical regions. The lesions may clear completely and leave no residua or progress to produce multiple cavities. The early roentgenographic changes may be confused with those of bacterial or viral pneumonia while the late ones may be difficult to distinguish from tuberculosis. Healed pulmonary coccidiomycosis is characterized by the presence of discrete, scattered, calcified nodular areas in the lungs.

The progressive form of coccidiomycosis, coccidiodal granuloma, develops in 1 out of 500 white patients; it is

sons. Monilia and Torula often increase markedly and become the predominant form in the pharyngeal flora as a result of antibiotic administration, without producing disease.

The course of pulmonary moniliasis or torulosis is usually short and terminates fatally. In some cases, however, the disease becomes chronic and may persist for months or years. There is no specific therapy for this type of infection. The administration of iodides may be of value. Before this drug is given, a skin test with *Monilia* or *Torula* antigen must be performed. If the reaction is positive, desensitization by repeated injections of a vaccine made from the organisms isolated from the sputum must be carried out. If the skin reaction is about 2 cm. in diameter, 1:100 dilution of vaccine is given; if it is about 3 cm., a 1:1000 dilution is used, and, if the zone of reaction is larger than this, the starting dilution is 1:10,000. The antigen is injected subcutaneously in an initial dose of 0.1 ml. of the appropriate dilution and increased by 0.1 ml. every other day until 1 ml. is being given. If an untoward effect appears, treatment must be interrupted for several days and resumed again with one-tenth the quantity responsible for the reaction. The administration of potassium iodide solution is started after vaccine has been given for 2 weeks. The initial dose is 1 drop 3 times a day. This is increased by 1 drop per day to a maximum of 20 drops 3 times a day. The quantity given is then gradually reduced to 3 drops 3 times daily, and then again increased to 20 drops 3 times a day. The last procedure is repeated once. *Torula* infections have been treated on an experimental basis with the antibiotic Amphotericin B, with some success. The dose of this agent is 0 25 mg. per Kg. given intravenously over a 6 hour period the first day. This is followed by 0.5 mg. per Kg. on the second, 0.75 mg. per Kg. on the third, 1.0 mg. per Kg. on the fourth day and daily thereafter for the next 3 to 4 weeks.

the lungs which reveals the residual, diffuse, nodular pulmonary calcifications. A positive skin reaction to *Histoplasma* antigen is usually present in these cases. Occasionally, however, invasion of the respiratory tract by *H. capsulatum* produces an acute pneumonitis in which fever, malaise, vague chest discomfort, non-productive cough, and dyspnea are the outstanding manifestations. A variety of changes in the lungs, depending on the extent of involvement, may be detected by physical examination; these do not indicate the etiology since they are identical with those present in many types of bacterial or viral pulmonary disease. The findings of roentgenographic study of the chest are also variable; increased bronchovascular markings, peribronchial infiltration, miliary or diffuse interstitial lesions, discrete or confluent areas of lobular consolidation, nodular granulomas, abscesses, cavities, and miliary calcifications have been described. The white blood count may be elevated, normal or depressed.

The diagnosis of acute pulmonary histoplasmosis must be considered in individuals with manifestations of acute infection of the respiratory tract who reside in an area where this disease is endemic; the incidence is particularly high in the midwestern part of the United States. Isolation of the fungus from the sputum by culture on Saboraud's or corn meal agar is the only method of establishing the diagnosis. A positive skin test, although suggestive, is often of little help because of the high frequency of such reactions in normal individuals living in endemic areas.

The prognosis is grave, and the fatality rate high, especially if the *Histoplasma* become widely disseminated and produce involvement of many organs. There is no effective treatment.

Pulmonary Actinomycosis and Nocardiosis

The source of pulmonary infection with *Actinomyces* is usually the mouth and throat. The organisms are present in

3.5 times more common in Mexicans and 14 times more frequent in Negroes. Lesions appear in bone (spine, pelvis, hands, and feet, most often), meninges, joints, brain, eyes, adrenal, myocardium, pancreas, prostate, spleen, liver, and lungs. The clinical pictures which appear depend on the location of the disease.

The differential diagnosis of pulmonary coccidiomycosis is difficult. The possibility of this disease should be suspected in patients with acute pneumonia or in those with chronic disease of the lungs who reside in an endemic area. The white blood count is usually elevated and may be 25,000 per mm^3 or higher; eosinophilia, ranging from 10 to 30 per cent, is frequent. The most important diagnostic procedure is isolation of the causative agent. This may be accomplished by culture of sputum or gastric washings treated for 4 hours with 0.05 per cent copper sulfate (final concentration) on Saboraud's or corn meal agar, or inoculation of these materials into guinea pigs (intratesticular) or mice (intraperitoneal). Skin test with coccidiodin (a filtrate of broth culture of *Coccidiodes*) is of value. The reaction becomes positive within 3 weeks after the disease starts. An abrupt change from negative to positive with a 1:1000 dilution is diagnostic of recent infection; this may occur in from 2 to 21 days after onset. Skin reactivity to coccidiodin may persist for as long as 10 years. Falsely positive tests are observed in histoplasmosis and blastomycosis. About 70 per cent of patients with disseminated coccidiomycosis have negative reactions even when concentrated antigen is used; the demonstration of a rising serum precipitin titer for the fungus is of help in diagnosis in these cases.

There is no specific treatment for coccidiomycosis.

Histoplasmosis

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Pulmonary Actinomycosis and Nocardiosis

The source of pulmonary infection with *Actinomyces* is usually the mouth and throat. The organisms are present in

the tonsils and around the teeth of some normal individuals. Either the aerobic form (*Nocardia*) or the anaerobic one (*Actinomyces*) may invade the lungs; both produce the same kind of disease. The early manifestations of pulmonary actinomycosis or nocardiosis are mild, irregular fever and cough productive of sputum which usually becomes purulent and may contain blood as the infection progresses. Pleuritic pain and pleural effusion appear in some cases. If the chest wall is invaded by the organisms, multiple sinuses are formed. As the process advances, loss of weight, weakness, anemia, spiking fever, night sweats, and dyspnea become prominent. In the early stages, the physical findings over the lungs are not striking and cannot be differentiated from those present in other acute pneumonias. Later, large areas of dullness appear, and the chest wall becomes retracted and limited in motion. X-ray usually reveals many smooth, irregular, large areas of consolidation with small, irregular areas of rarefaction but without cavity formation. The lesions are most often present in both lower lobes, although they may be unilateral or involve any part of the parenchyma. Pleural adhesions or effusion may be detectable. Invasion of the ribs may take place and produce destructive and proliferative changes.

The diagnosis of pulmonary actinomycosis is established by demonstration of the typical "sulfur granules" or tangled masses of branching gram-positive filaments in the sputum. *Nocardia* are acid-fast and may be confused with the tubercle bacillus. Culture of the sputum should be carried out under both aerobic and anaerobic conditions.

Treatment consists of the administration of penicillin. Doses of 500,000 to 1,000,000 units of benzyl penicillin G intramuscularly in divided doses daily have been found to be effective. Some physicians administer sulfadiazine simultaneously with the antibiotic. Surgical drainage of all accessible lesions is important. When the pulmonary disease

is localized and fails to clear with drug therapy, lobectomy or segmental resection must be considered.

Other Fungal Infections of the Lungs

A number of fungi other than the ones described above may cause pulmonary infection. With practically all of them, the acute phase of the disease may be difficult to differentiate from other types of pneumonia. However, unlike bacteria or viruses, the fungi tend to produce chronic lung involvement and are most easily confused with tuberculosis. Some of the organisms which are responsible for prolonged pulmonary disease are *Blastomyces* (blastomycosis), *Geotrichum* (geotrichosis), *Aspergillus* (aspergillosis), *Mucor* (mucormycosis) and *Sporotrichum* (sporotrichosis). The possibility of mycotic infection of the lungs must be considered in all cases in which chronicity is a feature, and the presence of tuberculosis cannot be established. The diagnosis is made by isolating the organisms from sputum by culture on Saboraud's or corn meal agar. There is no specific therapy for most of the infections The use of iodides and desensitization by the repeated injection of autogenous vaccines, as described for pulmonary moniliasis, is of value in some cases. Blastomycosis may be cured by the administration of stilbamidine (Chapter XV).

RICKETTSIAL PNEUMONIA

Although harassing, non-productive cough may be present in typhus fever or Rocky Mountain Spotted fever, localized pneumonitis or pulmonary consolidation due to the rickettsiae which produce these diseases are rare. Most episodes of pneumonia which complicate these infections result from secondary bacterial invasion and can be treated with antibiotics to which the causative organisms are susceptible. There is one type of rickettsial disease in which a skin

eruption does not appear and in which pneumonia is the only manifestation; this is Q fever.

Q Fever

Q fever is produced by *Coxiella burneti.* Infection is contracted by inhalation of contaminated dusts or the ingestion of milk or handling of materials harboring the organisms. The feces of a variety of ticks contain the rickettsiae. Sheep, goats and cows in the United States, and bandicoots in Australia are naturally infected. Q fever has been described in abbatoir workers, employees of stockyards, wool processors, and laundry workers in Texas, Illinois, Pennsylvania, Montana and New York. The disease has occurred in laboratory personnel studying the organism. It is not transmitted from man to man.

The incubation period of Q fever is 14 to 26 days. Headache, malaise, muscle aching, and fever (101-104°) with chilly sensations are the early features of the disease. After a few days, an unproductive cough appears. Physical examination reveals only scattered suppression of breath sounds and rales. X-ray study of the lungs shows the same type of changes as are present in "atypical viral pneumonia" In some patients the respiratory manifestations are so mild that they attract no attention, pulmonary involvement is detected only when a roentgenogram of the chest is made. The disease lasts from a few days to 2 weeks, although infiltration of the lungs may persist for a long time. In about 20 per cent of cases, signs and symptoms may still be present after 4 weeks; this is commonest in elderly individuals. Relapse occurs occasionally. Complications are uncommon. Secondary bacterial pneumonia is rare. Hepatitis with detectable jaundice appears in about one-third of the cases which are prolonged.

The diagnosis of Q fever depends on a high index of suspicion. Most important in suspecting the disease are an occupational history or residence in an endemic area within

a month of onset of symptoms. The clinical course and physical and roentgenographic findings are not diagnostic and are most often confused with "atypical viral pneumonia." The presence of Q fever is established by serologic study. Agglutinins for *Proteus* do not appear. An increase in complement-fixing antibody for *Coxiella burneti* when serums obtained in the acute and convalescent stages of infection are compared is specifically diagnostic.

Q fever is treatable. The agents of choice are tetracycline or chloramphenicol. A dose of 0.25 to 0.5 gm. of either of these agents given orally every 6 hours produces rapid cure in most instances; in some, however, the response is slow, and therapy must be continued for 2 or more weeks. Relapse occurs occasionally when treatment is stopped.

Pneumonia Due to Worms

Invasion of the lungs by *Ascaris*, *Strongyloides*, and *Trichinella* produces manifestations which are often very difficult to differentiate from bacterial or viral pneumonia. The parasites reach the pulmonary tissues by way of the blood stream. The possibility of this type of pneumonitis should be suspected in patients with obscure infections of the lungs who live in areas of the world where these worms are common. In the United States, *Trichinella spiralis* is the most frequent cause of "parasitic" pneumonia.

Trichinella Pneumonia

Pneumonia occurs in about 10 per cent of patients with trichinosis. It may appear at any time during the course of the disease and may be diffuse or have a lobular or lobar distribution. The outstanding manifestations are fever and cough which may be unproductive or accompanied by the expectoration of thick or bloody sputum. Pleuritic pain and pleural effusion develop in some cases. Physical and x-ray examination of the chest are not diagnostic because the

findings may be identical with those of invasion of the lun; by various bacteria or viruses.

When the characteristic manifestations of trichinosi severe myalgia and high grade eosinophilia, are presen the appearance of pulmonary involvement usually poses li tle diagnostic difficulty. Although bacterial pneumonia ma occur, this is usually accompanied by a sharp decrease c disappearance of eosinophiles from the circulating blooc *Trichinella* may invade the lung and produce disease, how ever, prior to the development of the typical muscle pai and blood abnormality. Since there is usually a leucocytosi with an increased number of neutrophiles at this time, th possibility of bacterial pneumonitis is suspected most frequently. The appearance of eosinophilia within a few days usually clears the confusion.

The diagnosis of *Trichinella* pneumonia is made clinically when other manifestations of trichinosis are present. It is confirmed by muscle biopsy or titration of serum precipitin for the parasite (Chapter XIV). Antibiotics are of value only if secondary bacterial infections of the lungs occurs. ACTH or adrenal corticosteroids may produce a dramatic effect when the pulmonary involvement is due to *Trichinella* (Chapter XIV).

Chemical Pneumonia, Pulmonary Involvement in Acute Rheumatic Fever, Infectious Mononucleosis and Erythema Multiforme Exsudativum (Stevens-Johnson Disease)

A picture of acute pulmonary disease readily confusable with bacterial or viral pneumonia may develop after inhalation of such chemical agents as kerosene, gastric juice, mineral oil, and beryllium. Although the latter two are most often responsible for chronic, progressive fibrosis of the lungs, they may also produce acute pneumonitis. The diagnosis of this type of disease is usually made on the basis of

a history of exposure; fat droplets may be observed in the sputum in cases of lipoid pneumonia.

Severe pulmonary involvement may occur in acute rheumatic fever. It is observed in 50 per cent of fulminating episodes, in 25 per cent of polycyclic attacks, and in 10 per cent of mild cases. The process is usually diffuse. Fever and cough are the outstanding symptoms. Hemoptysis, chest pain and pleural effusion are common. Dyspnea and cyanosis are observed in some cases. The white blood count is elevated with a relative increase in neutrophiles. The conditions with which rheumatic pneumonia is most easily confused are bacterial infection of the lungs and acute left ventricular failure; it may be very difficult to make a differentiation. The situation is made more complex by the fact that all three pulmonary processes may be present simultaneously in a rare case. The presence of cardiac decompensation may be ruled out by the demonstration of a normal venous pressure and circulation time. If pathogenic organisms are present in the sputum, it is imperative that an appropriate *antibiotic agent be administered promptly in adequate* quantity. The presence of large numbers of polymorphonuclear leucocytes in the sputum is of some help in suggesting superimposed bacterial infection.

About 10 per cent of cases of infectious mononucleosis develop pneumonia which is probably due to the agent responsible for the primary disease The symptoms, physical signs, and roentgenographic findings are not characteristic but are similar to those observed with many bacterial or viral infections of the lungs. Sterile pleural effusion is a very rare complication. The diagnosis is usually clinically apparent when other manifestations of infectious mononucleosis are present. It is confirmed by a rise in the titer of heterophile agglutinin in the patient's serum (Chapter VI). There is no specific treatment for this disease.

Pneumonia occasionally appears in the course of erythema multiforme exsudativum, a disease characterized by an

erythematous-papular or vesiculo-bullous eruption, stomatitis, and conjunctivitis. Sensitization to drugs (sulfonamides, barbiturates) and "viral" respiratory infection are the usual precipitating factors. Pulmonary involvement occurs in approximately 50 per cent of the cases which appear to be infectious in origin. The clinical manifestations and x-ray changes are indistinguishable from those of "atypical virus pneumonia." In some instances, it is impossible to determine whether the pulmonary disease follows the eruptive disorder, or vice versa. When the Stevens-Johnson variant of the syndrome is present (severe vesiculo-bullous rash and marked conjunctivitis), the accompanying pneumonitis is often severe and diffuse. In such cases the use of ACTH or adrenal corticosteroids may produce dramatic results. In some untreated cases, high fever, pulmonary manifestations, and skin and mucosal lesions may be intense and persist for as long as 2 weeks.

Lung Abscess

The bacteria responsible for pulmonary abscess reach the lung by aspiration from the mouth and upper respiratory tract (most common), deposition of septic emboli arising in various organs, and lymphatic transport (very rare). It is believed that abscess will not develop unless there is an underlying pulmonary lesion. Atelectasis and infarction are the two most important predisposing factors; the former is thought to be present in every case. Most lung abscesses are secondary either to operations on the mouth or respiratory tract, or to pneumonia. About 50 per cent of those in children follow tonsillectomy. Five to 6 per cent result from the inhalation of foreign bodies. Surgical procedures in the abdominal cavity, particularly those involving the gall bladder, may also precede the appearance of pulmonary suppuration because of the atelectasis produced by limitation of chest expansion by pain and tight bandages. Lung

abscess complicates bronchiogenic carcinoma in some instances. Approximately 85 per cent of cases in which no predisposing factor is detectable are thought to be related to gingival and dental infections.

The nature of the organism involved in the production of lung abscess is important in determining the anatomical and clinical features of the disease. The beta-hemolytic streptococcus, *Staph. aureus,* and the pneumococcus produce simple suppuration. Fusiform bacilli and spirochetes, acting together, are responsible for "anaerobic" abscess ("gangrene of the lung"); this type is observed most often when infection follows operations on the respiratory tract or dental extraction.

The clinical picture of lung abscess is usually characteristic About 1 to 3 weeks after an episode of pneumonia or an operation on the teeth or pharynx, a cough, which is at first dry and then becomes productive, appears Pleuritic pain gradually develops and may become very severe; this is often the most striking symptom. Fever, of varying degree, is always present; it is frequently remittent or intermittent, but may be sustained at a high level. Dyspnea and cyanosis become apparent as the disease progresses, in some cases. Physical examination of the chest may be unrevealing except for limitation of motion of the affected side. If the abscess lies well below the pleura, no abnormal findings are detected. If it is situated close to the pleura, suppression of breath sounds, dullness to percussion, and a friction rub are often present in the involved area. Amphoric breathing and a positive coin sign are detectable when the abscess has become excavated and contains air. With drainage through the connecting bronchus, the sputum becomes purulent; it contains polymorphonuclear leucocytes and bacteria and does not have a foul odor. Slight to moderate hemoptysis may occur.

When fusiform bacilli and spirochetes are the cause of lung abscess, patients usually appear more severely ill than

when pyogenic infection is present. The pulmonary process is characterized by high, "spiking" fever and the expectoration of copious quantities of sputum which is gray in color and has the typical foul odor of rancid butter.

X-ray examination of the lungs in the early stages reveals only infiltration which is indistinguishable from pneumonia. As localization takes place, a rounded density surrounded by an irregular area of decreased radioluscence becomes apparent. When the abscess drains through the connecting bronchus, air becomes trapped in the cavity and a fluid level is detectable.

Since most lung abscesses lie within 1 cm. of the pleural surface, penetration into the pleural space with the production of empyema is common. When aerobic organisms are the causative agents, the fluid is purulent (*Staph. aureus* and pneumococcus) or serosanguinous (beta-hemolytic streptococcus). With fusospirochetal infection, it is thin, gray in color, and has an overpowering odor. The bacteria responsible for the empyema are easily demonstrated in the fluid by gram-stained smears.

The diagnosis of lung abscess is suspected in patients who, after an episode of pneumonia or a surgical operation in the mouth or throat, develop fever, cough productive of purulent or putrid sputum, and localized pleuritic pain. Demonstration of a rounded density surrounded by an area of infiltration or a cavity with a fluid level by x-ray examination of the lungs is confirmatory. The etiology of the lung abscess is established by bacteriological study of the sputum and pleural fluid. Culture on blood agar reveals the organisms responsible for the pyogenic type of disease. In "gangrene of the lung," gram-stained smears reveal myriads of fusiform bacilli and spirochetes; cultures are not practical because of the difficulty of growing these highly anaerobic organisms.

There are three approaches to the treatment of localized suppurative disease of the lung. (1) *Postural Drainage:*

When the abscess is connected with a bronchus, as shown by the expectoration of sputum, *the institution of postural drainage* is very helpful in emptying the pulmonary lesion and the bronchial tree of exudate. This is of no value in cases in which closed abscesses are present. (2) *Bronchoscopy:* This procedure, although not necessary in every case, *may be of help in the removal* of (a) secretions that cannot be eliminated by postural drainage, or (b) mucous plugs or foreign bodies responsible for atelectasis. It may also reveal the presence of an unsuspected bronchiogenic carcinoma. (3) *Chemotherapy:* The administration of antimocrobial agents often produces very dramatic results. Penicillin is the agent of choice for the therapy of lung abscess. A dose of 250,000 to 500,000 units of benzyl penicillin G intramuscularly every 6 hours is usually adequate, except when staphylococci resistant to the antibiotic are involved; in such cases, the sensitivity of the organism to various drugs must be determined and the agent to which it is most susceptible administered. When empyema is present, thoracentesis should be carried out, and 50,000 to 100,000 units of aqueous penicillin dissolved in 50 to 100 ml. of physiologic saline injected into the pleural space; this procedure usually *does not require repetition.*

Although the need for surgical drainage of lung abscess has decreased markedly since potent chemotherapeutic agents have become available, this type of treatment is still necessary in some cases. If the pulmonary lesion is not showing satisfactory evidence of regression with "medical" therapy over a period of 4 weeks, extirpation of the disease by lobectomy or segmental resection must be considered. When the empyema fluid is thick or collected in pockets, the intrapleural instillation of a mixture of 200,000 units of streptokinase and 50,000 units of streptodornase once daily for 2 to 3 days may be helpful. In some instances, marked thickening of the pleura develops despite therapy, and decortication of the involved lung must be carried out.

Tuberculosis

Man may be invaded by either the human or bovine type f tubercle bacillus; a rare case may be due to the avian train. In the United States, the commonest mode of infecion is direct contact with an individual with active disease, r with contaminated urine or wet or dry sputum.

Certain differences in the response of the host to tubercuous infection are related to non-specific factors. The fact iat tuberculosis is very common, but death relatively infreuent, suggests that, on the whole, man is capable of conining the infection to some degree. Age is a very important eterminant of the course of the disease. Young children are iost liable to disseminated infection shortly after invasion y tubercle bacilli; the fatality rate in this group is higher id the disease more rapidly progressive than in older idividuals. The risk of death is generally low between the ge of 5 years and adolescence. It then increases abruptly aching its height in patients 20 to 35 years old, especially males There is a second peak of incidence and death in ersons over 60 years of age, particularly males. Other facrs may also condition the response to invasion by *M. iberculosis*. Although the relationship of immunity and iberculin hypersensitivity is still in debate, many investiitors are of the opinion that these phenomena are insepable, and that one cannot be present without the other. hat animals insensitive and sensitized to tuberculoprotein have differently when exposed to infection is amply monstrated by the Koch reaction. When tubercle bacilli e injected endermally in healthy guinea pigs, a local cer develops slowly. Dissemination of the organism to the gional lymph nodes from which they are carried by way the blood stream to all parts of the body is rapid. If the ocedure is carried out in an animal previously infected ith the tubercle bacillus, a large ulcer develops rapidly in e area of injection but the organisms do not migrate be-

yond the regional lymph nodes. This observation suggests that the ability of the host to localize tuberculosis and prevent the disease from becoming widespread is related to the presence of tuberculin hypersensitivity. On the other hand, it has been shown that immunity is still present in guinea pigs after the tuberculin reaction has been abolished by desensitization.

Heredity is important in determining the outcome of tuberculosis. The relative resistance and low fatality rates in Jews and high degree of susceptibility to far advanced disease and death in Negroes are good examples of the role of this factor. This has also been demonstrated experimentally by the development of strains of rabbits with high and low degrees of resistance to tuberculous infection through selective breeding. Nutritional status and environmental factors may be of significance in altering the risk of invasion and response to infection. For example, tuberculosis increased in frequency in the concentration camps in Europe during the last war in direct proportion to the prevalence of severe malnutrition. Pregnancy also influences the course of the disease; in most cases, it tends to be mild but, in some, it is aggravated. Very frequently, the severity increases abruptly shortly after parturition. Diabetes mellitus and congenital pulmonic stenosis are associated with an increased incidence of tuberculosis. Individuals with mitral valvular defects tend, in general, to have mild disease when they are infected. Activation and extension of a latent focus of tuberculosis in the lungs may follow pneumonia or lung abscess involving the area in which the lesion is present.

When tubercle bacilli are inhaled by a susceptible individual, they settle in the alveoli and provoke an immediate outpouring of polymorphonuclear leucocytes. This is followed within a short time by infiltration of lymphocytes and endothelial cells which fuse to become giant cells. Fibroblasts invade, and the lesion then possesses all of the features which characterize the primary or solitary tubercle

—a few neutrophiles, endothelial and giant cells, and early fibrosis. Usually more than one tubercle develops; these fuse to form the conglomerate tubercle. Involvement of the lymphatic vessels and hilar lymph nodes by the tuberculous process occurs and completes the triad of lesions which constitutes the Ghon complex—the pulmonary parenchymal infiltrate (usually located subpleurally in one of the lower lobes), lymphangitis, and lymphadenitis. Sensitization to tuberculoprotein takes place within 5 to 6 weeks after infection and the tuberculin test becomes positive. In most cases, the Ghon complex heals by fibrosis and finally becomes calcified; this is characteristic of "primary" tuberculosis. In some instances, however, the pulmonary process progresses and the peribronchial and peritracheal lymph nodes become markedly enlarged. Erosion of the trachea and bronchi with the production of tuberculous ulcers may occur, or the infected softened lymph nodes may rupture into blood vessels resulting in widespread hematogenous dissemination of the organisms and the development of miliary disease. The endobronchial lesions may be responsible for spread of disease either by way of the blood stream or via the airway. Hemoptysis may occur in primary tuberculosis and is associated with the bronchial ulcers or extension and cavitation of the area of involvement in the pulmonary parenchyma.

"Secondary," "adult," or "reinfection" tuberculosis differs from the primary form in several respects. (1) It occurs in patients already sensitized to tuberculoprotein. (2) Involvement of upper lobes is the rule; basilar disease tends to occur most often in diabetics. (3) The pulmonary lesion behaves in a fashion similar to that observed when the Koch phenomenon is produced in an animal previously exposed to tubercle bacilli; rapid ulceration with extension to lymph nodes takes place in all cases, but hematogenous dissemination is uncommon. Whether infection is exogenous or endogenous in origin is a debated question; many investigators are of the opinion that the latter is most frequent.

The clinical picture of tuberculosis is very variable. The disease may be so mild that the patient and his physician are totally unaware of its presence until it is discovered by "routine" chest x-ray, or *the conversion of a negative to a* positive tuberculin reaction. This is very often the situation in "primary" tuberculous infection which most frequently subsides spontaneously. When tuberculosis is clinically evident, the outstanding manifestations are fever, night sweats, loss of weight, anorexia, persistent cough, and hemoptysis. Some cases run a very fulminating course, "galloping consumption", which rapidly leads to death, unless recognized and treated. In a moderate number of instances, the first sign of the disease is a "sterile" pleural effusion which contains primarily lymphocytes, increased protein, and occasionally blood. Tuberculosis of the lungs may be very atypical in elderly persons in whom the only manifestation may be "asthma" or exaggeration of a chronic "cigarette cough." The sudden appearance of laryngitis with chronic hoarseness may be the first sign of tuberculosis involvement of the larynx and lung. The presence of pulmonary tuberculosis may be first suspected only after meningitis due to the tubercle bacillus develops, bronchiectasis of an upper lobe is detected, or bronchostenosis is revealed by bronchoscopy in an "unresolved" pneumonia. Patients with vague symptoms of malaise, ease of fatigue, loss of weight and cough, young females in whom the menstrual cycle becomes abnormal, and individuals who have recurrent or prolonged episodes of an illness simulating influenza, "virus pneumonia", or "grippe" should be studied for tuberculosis. An "unresolved" pneumonia, cough and expectoration persisting for several weeks, hemoptysis of any degree, unexplained fever, chronic lymphadenopathy, fistulo-in-ano, or "sterile" pleural effusion may be the only manifestations of the disease.

Physical examination of the chest may be completely unrevealing, this is true in both the primary and minimal types and even in moderately far-advanced pulmonary tubercu-

losis. In the child, the only finding may be d'Espine's sign indicating enlargement of the tracheobronchial lymph nodes. The detection of post-tussive subclavicular rales is very important in suspecting the disease. In far-advanced and in long-standing involvement, numerous abnormal physical findings may be elicited. Inspection of the chest wall often reveals atrophy of the infraclavicular and supraspinatus muscles on the affected side; limitation of motion with expiration may also be present. The percussion note over the lesion may be dull or hyper-resonant. Suppression of breath sounds or bronchial breathing as well as other signs of consolidation may be detected. When a cavity has developed, the breath sounds over it are amphoric in quality and the "coin test" is positive. Pleural effusion produces the findings usually associated with fluid in the chest; most significant is the fact that the trachea and other mediatinal structures are pushed to the opposite side. Endobronchial disease with obstruction is accompanied by wheezing and, if the occlusion is sufficiently marked, the findings of atelectasis. It is important to stress that any or all of these physical findings may be present with other acute and chronic infectious or non-infectious disorders of the lung.

The white blood count in tuberculosis is variable. As a rule, it is normal with minimal and chronic productive lesions; a relative lymphocytosis is detectable in some cases. In far-advanced disease or when the exudative phase is predominant, leucocytosis and increase in neutrophiles is common; a leukemoid reaction may occur occasionally and cause diagnostic confusion. Anemia, usually of the hypochromic, microcytic type, is a frequent feature in rapidly progressive or long-standing active cases.

X-ray examination of the lungs, while highly suggestive of the presence of tuberculosis, does not rule out the possibility of other diseases. An infraclavicular infiltration of 1 cm. or greater in diameter is presumptive evidence of a tuberculous process but may represent other lesions, includ-

ing tumor. The detection of cavitation (planigrams are often necessary) directs attention first to the possibility of infection by the tubercle bacillus. However, the same finding may be noted in chronic coccidiomycosis, Friedlander bacillus pneumonia, actinomycosis, and nocardiosis, in all of which involvement of upper lobes is common. Apical bronchiectasis is often tuberculosis in origin but may be due to other causes. The presence of calcification is of help in distinguishing tuberculous lesions from bronchogenic carcinoma in which it is seldom, if ever, present. In some instances, the exact etiology of a pulmonary process can be established only by exploratory thoracotomy. X-ray study of primary tuberculosis is often totally unrevealing. A parenchymal infiltrate, usually in one of the lower lobes, may be observed in some cases. Enlargement of the hilar nodes is apparent occasionally. In healed cases, an area of calcification in the lung and the presence of calcium in the draining lymph nodes may be observed.

The clinical course of tuberculosis, although variable, is most often characterized by intermittent but steady progression. In "primary" infections, spontaneous healing with fibrosis and calcification of the pulmonary and lymph node lesions is most frequent, although extension of the process may occur in both areas and lead to widespread local or disseminated disease. In children under 2 years of age, there is a constant risk of miliary tuberculosis or meningitis, or both. In the "adult" type of infection, spread through the involved lung is slow, and there is a predominant tendency to fibrosis. This may go on for many years and finally lead to emphysema, severe dyspnea, and chronic invalidism. Most commonly, progression is more rapid and either steady or intermittent. Each episode of extension may be accompanied by minor, non-specific, constitutional manifestations. All varieties of lesions develop in the lungs—exudative, fibrotic, cavitary, and bronchiectatic. In almost all instances the infection spreads to the other side by way of the bron-

chial tree. Dissemination through the lymphatics may also occur, or the lungs may bear the brunt of a tubercle bacillemia. The eventual outcome in many of these cases is death. Occasionally, acute tuberculous pneumonia develops. This is most common in Negroes and elderly people and is almost always secondary to a cavity lesion. The symptoms and signs are the same as those of a severe bacterial pneumonitis; lobular and lobar consolidation are common.

Although the diagnosis of tuberculosis may be strongly suspected on the basis of clinical manifestations and roentgenographic findings, it can be definitely established only by laboratory study. In some age groups, the tuberculin reaction is of help. The demonstration of tuberculin sensitivity in adults usually indicates previous contact with the tubercle bacillus and is not related to activity of the disease. In young children, especially those under 3 years of age, on the other hand, a positive reaction is practically always associated with active infection. Most important is the conversion of tuberculin negativity to positivity while a patient is under observation. Examination of sputum, gastric washings, and material aspirated from the bronchial tree for acid-fast organisms is the most important diagnostic procedure. Acid-fast stained smears may, however, be misleading. About 10 per cent of gastric washings and 1 per cent of sputa contain acid-fast organisms which are not *M. tuberculosis;* many of these are saprophytes present in food, water, soil, and air. In addition, *Nocardia* may be mistaken for the tubercle bacillus because it has the same staining properties. Cultures and inoculation into guinea pigs must be carried out. The writer prefers to do both in every suspected case because animal inoculation yields positive results in some cases when cultures are negative and vice versa. That isolation of the organism is necessary to prove the presence of tuberculosis is emphasized by the inaccuracy of smears, the fact that staining procedures may fail to reveal organisms, and the increasing number of cases in which pulmonary disease in-

distinguishable from tuberculous infection are being proved to be due to *Nocardia* and chromogenic acid-fast organisms. Bronchoscopic study and biopsy of endobronchial lesions for bacteriologic and anatomic investigation are necessary in some instances. The value of pleural biopsy in establishing the cause of an idiopathic pleural effusion has been stressed recently.

The treatment of pulmonary tuberculosis has undergone radical change in the past 10 years. One of the procedures which has been subjected to close scrutiny is bed rest. There is now more or less general agreement that patients with minimal pulmonary involvement may be allowed to be ambulatory to an almost normal degree if they are treated with antituberculous drugs. In some quarters, this has been the practice even in far-advanced, "open" cases. Some clinicians still insist, however, on strict bed rest in such instances. It appears clear, nevertheless, that some degree of ambulation *is probably desirable and does not have a deleterious effect* on the disease. Patients with more than minimal infections who are receiving tuberculostatic agents may be allowed to sit in a chair for a varying period each day, walk about their room a little, and have bathroom privileges. After 3 to 6 months of such restricted activity, gradual physical rehabilitation is undertaken. This is the conservative approach and is probably best to employ until more evidence becomes available indicating the lack of necessity of any type of bed rest, regardless of the severity of pulmonary tuberculosis.

Confinement of patients with tuberculosis to sanitoria is gradually being given up. Most cases are now treated at home, although some are hospitalized for a short period until the diagnosis is established and therapy initiated. While the *socio-economic and psychological advantages of* this procedure are unquestionable, the possibility of spread of disease to contacts is a very important consideration which must be uppermost in the minds of the patient, his family, and his physician. If the situation at home can be arranged

so that the infected individual can be isolated, aseptic precautions can be practiced, and there are no young children in the family, treatment outside the hospital is practical. If, however, the patient has an open cavity from which he is expectorating tubercle bacilli, and he cannot be properly isolated in the household, confinement to a hospital for the first 3 months of drug treatment seems a much safer approach. Most important is the problem of transmission of disease to young children because of their susceptibility to widespread infection and death. The writer does not allow persons with active tuberculosis to be treated in a home where youngsters are residing, except under unusual circumstances. Cases which are not excreting organisms may be managed at home with less concern for the safety of the family, but isolation should be carried out until arrest of the disease has been proved. Both the welfare of the patient and his disease and the possibility of transmission of infection to contacts must be considered when the question of treatment at home is raised. The latter must not be overwhelmed by the enthusiasm for making the life of the patient easy, comfortable, and "normal."

The keystone of treatment in tuberculosis is chemotherapy. Although different regimens have been used, and opinion has not yet crystallized concerning optimal therapy, it is agreed that the simultaneous administration of at least 2 drugs produces better results than the use of any agent alone The combinations of agents most widely used are (1) streptomycin plus para-aminosalicylic acid (PAS), (2) PAS plus isonicotinic acid hydrazide (INH), and (3) streptomycin plus INH. The latter is the regimen most recently recommended by the Veterans Administration. The initial dose of PAS is 1 gm. every 4 hours; this is increased, within a week, to 12 gms. in divided doses, per day. INH is given at a level of 8 mg. per Kg. per 24 hours. When streptomycin is employed, 1 gm. is injected intramuscularly twice a week. The administration of 100 mg. of pyridoxine daily reduces

the risk of neurologic complications produced by INH. Treatment should be continued for at least one year, regardless of the combination of drugs used; in some cases, it may have to be prolonged beyond this point. The risk of death in tuberculosis has been sharply reduced by chemotherapy. It must be kept in mind at all times, however, that the decreasing fatality rate is not associated in many areas with a decline in the incidence and prevalence of the disease. This emphasizes the constant necessity for careful case-finding among contacts of persons with active disease and proper management of newly discovered infections.

The management of "primary" or childhood tuberculosis presents a number of problems which will be solved only by long-term, carefully controlled investigations. The following practices have been recommended by experienced clinicians and appear entirely sound.

(1) Children with conversion to a positive tuberculin but no clinical or roentgenographic evidence of tuberculosis have a fatality rate of 1.5 to 3 per cent. Opinion differs regarding the necessity for treatment but many such youngsters are being given tuberculostatic drugs. The tuberculin reaction becomes negative in some instances after therapy.

(2) Children less than 3 years old should be treated even in the absence of a demonstrable pulmonary lesion. The fatality rate in those in whom pulmonary infiltration is observed is 60 per cent, in those in whom x-ray of the lungs is negative, it is 7 per cent when therapy is not given

(3) In patients 3 to 12 years old, tuberculostatic agents should be administered only when clinical manifestations such as fever, cough, anorexia, loss of weight, etc are present or a lesion is detected by x-ray study of the lungs. Some clinicians treat all such children, even in the absence of signs and symptoms of active disease, purely on the basis of the conversion of a negative to a positive tuberculin reaction; whether this is advisable is questionable.

Surgical treatment is indicated in many cases of pulmonary

tuberculosis, especially those in which cavity closure does not take place or is incomplete, or infection is persistent and producing respiratory crippling. *Determination of ventilatory efficiency must be made prior to surgery in every case.* All patients should receive tuberculostatic drugs prior to and after operation. The decision as to the type of procedure —segmental resection, lobectomy, or pneumonectomy—must be left to the experienced thoracic surgeon.

The term "arrested" requires re-definition since chemotherapy for tuberculosis has become available. In the pretreatment era, a case was considered "arrested" when no change in the pulmonary lesion was demonstrable by *repeated x-ray study over a period of 6 months.* Since the tuberculostatic agents stop progression, it is impossible to draw conclusions concerning stabilization of the process *while therapy is being given, as long as regression is taking* place, "arrest" is not present. The writer has adopted the following condition for considering patients who have received drugs "arrested": *complete stability of the infiltrate* in the lung for 6 months *after discontinuation of all treatment.*

The reduction in the fatality rate of tuberculosis by the tuberculostatic drugs is striking. Unfortunately, however, this has led to the completely erroneous inference that *tuberculosis is a vanishing problem. Nothing could* be further from the truth. The disease is still a very important one. As a matter of fact, it is increasing in incidence and prevalence *in some areas despite the effective management of* detected cases. Neither the public nor physician can become complacent about tuberculosis. It is just as imperative at present, *as it was in the days* when the tuberculostatic drugs were not available, to carry out all of the measures of importance in detecting new infections and preventing spread of the *disease.*

The practical value of BCG vaccination as a prophylactic measure in tuberculosis is still controversial. There seems to

be no doubt that in certain groups of highly susceptible people the use of BCG has been very effective in decreasing the risk of infection and ameliorating its course when it occurred. However, in areas of the world where good case-finding and proper treatment of the active disease are being carried out, the incidence of tuberculosis in the general population is decreasing at just as rapid a rate as in those areas in which BCG has been employed extensively. One of the great difficulties in attempting a critical evaluation of this immunization procedure is related to the lack of standardization of the vaccine. Until an adequate number of carefully-controlled studies in which standardized antigen is used are carried out, it is impossible to make a critical evaluation of the effectiveness of BCG in the prevention of tuberculous infection.

CHAPTER VIII

INFECTIONS OF THE MEDIASTINUM, PERICARDIUM HEART, AND BLOOD VESSELS

MEDIASTINITIS

Acute Mediastinitis

Acute infections of the mediastinum may follow viral or bacterial diseases of the lung, the introduction of organisms from the upper respiratory tract, or rupture of the esophagus or a bronchus. In some instances of viral laryngotracheobronchitis, involvement of the tracheobronchial lymph nodes takes place and produces a mild mediastinitis in which fever, a sense of retrosternal discomfort, and poorly defined dull aching in the central and upper parts of the chest are the outstanding manifestations. Acute non-suppurative mediastinitis may follow or accompany pneumonia, "pleurisy," or pericarditis. The signs and symptoms are similar to those present with suppuration, but are much milder and usually clear without specific therapy. Pyogenic infection of the mediastinum produces either a diffuse, spreading inflammatory reaction or an abscess. This may be secondary to (1) carcinoma of the bronchus with perforation, (2) retropharyngeal abscess (children under 3 years of age), (3) cervical abscess, (4) Ludwig's angina, (5) pneumonia or empyema, (6) osteomyelitis of any area of the thoracic

cage, (7) rupture of the esophagus as a result of peptic esophagitis, attempts at esophagoscopy, dilatation of strictures, swallowing sharp objects, bullet or knife wounds, or retching or vomiting. Anterior mediastinitis most often follows disease in the neck, while involvement of the posterior portion results from suppuration of mediastinal lymph nodes or pulmonary infection.

Acute mediastinitis is most frequently due to *Staph. aureus*, although any gram-positive or negative bacteria may be involved, depending on the mechanism of infection. The *fusospirochetal group is often responsible when perforation* of the esophagus occurs If the process is secondary to Ludwig's angina, the beta-hemolytic *Streptococcus* may be the causative agent. Any organism normally present in the mouth or upper respiratory tract may produce the disease.

The clinical picture of acute mediastinitis is a composite of the general manifestations of infection plus signs of compression of any of the structures in the mediastinum. Fever of varying degree, often spiking and accompanied by chills, is almost universal. The patient appears acutely and severely ill. High grade leucocytosis with a marked increase in polymorphonuclear leucocytes is the rule. Pain in the anterior, central, or substernal areas of the chest, often radiating upward in the neck or back, is common. Swallowing frquently produces discomfort. Respirations are shallow, and cough may be prominent.

Physical examination usually reveals retrosternal dullness to percussion except in cases in which large amounts of gas are produced by the infecting organism; in the latter, the percussion note may be normal or hyper-resonant. Hamman's sign, a precordial crunching noise synchronous with the heart beat, is detectable when air is present in the mediastinum. Dissection into the neck produces subcutaneous emphysema. Localized redness and edema of the skin over the anterior chest wall is sometimes observed. In some instances, *tenderness to palpation can be elicited in the supra-*

sternal notch, supraclavicular areas, the jugular notch, around and below the xiphoid, and in the back, depending on the location of the abscess.

Signs and symptoms of pressure on mediastinal structures may be entirely absent if the abscess is small, or the diffuse inflammatory reaction mild. Abscesses which are of appreciable size or are strategically located, and large collections of gas produce a variety of manifestations. The clinical pictures which develop are related to the location of the lesion and the structures on which it impinges. When the superior vena cava is compressed, cyanosis, dilatation of the veins of the face, neck, and upper thorax, exophthalmos, congestion of the conjunctivae, and edema involving the lower face, neck, shoulders, arms, and upper thorax ("edema of the little fur cape") are the striking features. Pressure on the heart may produce decreased cardiac output, pulmonary edema and arrythmias. Inequalities of the radial and carotid pulses are observed when the aorta is involved. Paralysis of one vocal cord follows impingement on the recurrent laryngeal nerve. Dyspnea, cough, and "croupy" breathing suggest obstruction of the trachea, while difficulty and pain on swallowing indicate narrowing of the esophageal lumen. Chylothorax or chylous ascites follows occlusion of the thoracic duct in its course through the mediastinum. If the vagus is affected, bradycardia is present; phrenic nerve involvement leads to loss of movement of the diaphragm. A Horner's syndrome—unilateral miosis, ptosis of the eyelid, and anhydrosis of the skin of the face—results from pressure on the stellate ganglion.

X-ray examination of the chest in patients with acute suppurative mediastinitis may show very little in the early stages; with severe disease, streaked or translucent areas overlying the mediastinal structures are detected. In cases which follow perforation of the esophagus or a bronchus, or those in which gas-forming organisms are concerned, air

and fluid levels are present in the mediastinum which is widened.

Acute suppurative mediastinitis is a very serious disease and requires early recognition and intensive treatment. Until definitive bacteriologic studies are completed, penicillin is the best agent to administer. From 5 to 10 million units of benzyl penicillin G per day (in divided doses intramuscularly every 3 to 4 hours) should be given as soon as the presence of mediastinitis is suspected. When the results of cultures become available, it may be necessary to change to another drug. For example, if a penicillin-resistant *Staphylococcus* is present, it is best to treat with chloramphenicol plus erythromycin (0.5 gm. of each every 6 hours) until the sensitivity of the organism to various antibiotics has been determined. Patients should be seen by an experienced thoracic surgeon as soon as the diagnosis is made, especially in instances in which the mediastinal infection is secondary to rupture of the esophagus or a bronchus. In addition, it may become necessary to institute drainage of the mediastinum because of a life-threatening degree of compression of the heart or vascular tree. The infection may fail to respond to antimicrobial therapy as long as introduction of organisms through holes in the esophagus or bronchus continues. Surgical closure is necessary in these cases.

Chronic Mediastinitis

Chronic inflammatory reaction or abscess in the mediastinum is rare. It follows pyogenic infection of the mediastinum or neighboring structures, actinomycosis, blastomycosis, or syphilis, but is most often secondary to tuberculosis. A fibrinous form of the disease is associated with pericarditis, aortic aneurysm, "pleurisy", and various types of infection of the lungs or thoracic cage. Tuberculous tracheobronchial lymph nodes may caseate and coalesce to form large mediastinal masses, or break down, liquefy, and empty into the

mediastinum forming a "cold" abscess which tends to perforate and form sinuses in the chest wall. Mediastinitis may also be secondary to tuberculosis of the sternum, ribs or spine.

The signs and symptoms of chronic mediastinitis are variable; their nature depends on the type and location of the lesion. With tuberculous infection, clinical manifestations are often absent or only mild. The syndrome may present itself as prolonged, obscure fever without localizing signs. If the mass is large and located anteriorly, widening of the mediastinum and dullness to percussion are prominent. Chronic disease of the posterior mediastinum is accompanied by paravertebral dullness to percussion. Signs and symptoms of compression of any of the mediastinal structures may develop and are similar to those observed with acute infections. X-ray examination of the chest often reveals discrete masses in the mediastinum which is usually wider than normal.

Chronic mediastinitis may be difficult to distinguish from tumors of the lungs with metastases to the tracheobronchial lymph nodes or from lymphoma involving these structures. The possibility of tuberculosis must be considered in every case since this is a treatable disease. The detection of tuberculous infection elsewhere, especially in the lung, or a positive tuberculin reaction in a young child are strong presumptive evidence in favor of this possibility. If sinus formation is present, a search should be made for tubercle bacilli and *Actinomyces*. A positive serological reaction for syphilis does not prove that this disease is responsible for chronic mediastinitis; a favorable response to antiluetic therapy establishes this diagnosis.

The treatment of chronic mediastinitis depends on its etiology. The therapy for tuberculosis in this area is the same as that employed in the pulmonary form of this infection (Chapter VII). If healing does not occur with chemo-

therapy, surgical eradication of the infected lymph nodes is indicated.

PERICARDITIS

Acute inflammation of the pericardium may be produced by a number of factors. There are at least 9 causes for pericarditis: (1) *Viral infection:* this is responsible for most cases of acute, benign, serofibrinous pericarditis; (2) *Hypersensitivity Reactions;* (3) *Tuberculosis;* (4) *Rheumatic fever;* (5) *Bacterial infection:* the most common organisms are *Staph. aureus,* the beta-hemolytic streptococcus, and the pneumococcus; (6) *Trauma;* (7) *Uremia;* (8) *Myocardial infarction;* (9) *Tumors.*

Although the manifestations of acute pericarditis vary quantitatively, the signs and symptoms which appear are qualitatively similar, regardless of the etiology. Pain is extremely variable in degree. When pericardial involvement without pleuritis is present, the discomfort is dull and oppressive in character, located below the lower end of the sternum and in the epigastrium, and relieved by pressure on the anterior chest; patients are inclined to lean over the edge of a table to produce relief. When the pleura is involved at the same time, as is the case in many instances of "viral" and some of suppurative pericarditis, the pain is sharp, knife-like, and exaggerated by breathing, swallowing and movement. A pericardial friction rub synchronous with the heart beat is detected in pericarditis; a pleural rub is heard, in addition, when pleuritis is present. Fever, chills, malaise, and leucocytosis are common but vary in degree with different types of pericardial infection. The development of an effusion in the pericardial sac may produce cardiac tamponade and signs of compression of other mediastinal structures. Dyspnea, edema, ascites, right upper quadrant pain due to acute congestion of the liver, and dysphagia resulting from pressure on the esophagus may

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Roentgenographic study of the chest in cases of pericarditis in which effusion is not present reveals no abnormalities of the cardiac silhouette. When fluid appears, increase in diameter of the heart shadow is prominent, but may be impossible to differentiate from cardiac dilatation or hypertrophy. *Fluoroscopic examination should be carried out in every instance.* With pericardial effusion, diffuse diminution in the intensity of the beat, increase in the size of the heart when the patient is lying down and a decrease when he sits up are frequently noted. These findings may also be detected, however, in some instances of cardiac dilatation or hypertrophy.

Certain electrocardiographic abnormalities are highly suggestive of acute pericarditis. These are probably not due to the pericardial inflammatory reaction but result from involvement of the underlying myocardium. During the acute stage of the disease, elevation of the S-T segment in one or more, or all, of the ECG leads is characteristic. There is no compensatory depression of S-T waves, this helps in the differentiation from early myocardial infarction. As pericarditis progresses, the S-T segments become lowered toward the isoelectric line and the T waves gradually become inverted. The sequence of elevation of S-T in some leads, without reciprocal depression in others, followed by return to the level of the *isoelectric line at the same time that the* T waves are inverting is diagnostic of acute pericarditis Absent R waves and deep Q waves, frequent findings in myocardial infarction, are not observed It may, nevertheless, be very difficult to distinguish the two conditions in the *very early stages; serial electrocardiographic studies* are necessary. When large pericardial effusions develop, the most striking finding is a marked decrease in voltage of all complexes in both the chest and limb leads.

The diagnosis of acute pericarditis is first suspected on the basis of the clinical findings described above. Electrocardiographic and x-ray studies are confirmatory. Although the

appear. In the absence of compression of the heart, shortness of breath may be due to pulmonary congestion, narrowing of the trachea and bronchi, or reduction of vital capacity resulting from encroachment of the effusion on the lungs and available intrathoracic space. Cough may be prominent; it is due to pressure on the trachea and bronchi or pulmonary nerve plexuses, or is a feature of the pulmonary disease which sometimes precedes or accompanies the pericarditis.

Physical examination in the acute phase, before effusion has developed, usually reveals only the general signs of infection and a friction rub synchronous with the heart beat over the precodium; abnormal findings may be elicited over the lungs when pericardial involvement is secondary to a pulmonary process. The friction rub present in the early stage frequently disappears as fluid collects in the pericardial sac; it may persist, however, because adhesions prevent separation of the layers of the pericardium. With large effusions, the cardiac sounds are distant and faint, and the apical impulse difficult to palpate. Ewart's sign, resulting from compression of the lung, may appear; the findings are those of consolidation (dullness to percussion, bronchial breathing, whispered pectoriloquy, increased tactile and vocal fremitus, and egophony) at the inferior angle of the left scapula Manifestations of cardiac tamponade resulting from decreased output may develop, the important signs are increasing peripheral venous pressure and progressive arterial hypotension with narrowing of the pulse pressure. If treatment is not instituted, shock appears. Paradoxical pulse is another important sign of pericardial effusion. A slight decrease of pulse pressure on inspiration is detectable in normal people. This is exaggerated when fluid is present in the pericardial sac, the volume of the radial or brachial pulse being appreciably less during the inspiratory phase of respiration. This is best determined with a sphygmomanometer, noting the level of arterial pressure at which the pulse is heard or palpated during inspiration and expiration.

start abruptly and be quite severe, or be very mild in the beginning and become progressively worse. The discomfort is aggravated by breathing, coughing, swallowing, or rotation of the upper part of the trunk. It is substernal or precordial in location and may radiate to the interscapular area, neck, epigastrium, or the left arm when it is often confused with myocardial infarction. The duration of the pain is variable; it may be present for only several minutes or may persist as the most prominent feature of the disease for several weeks.

Fever is present in practically all cases, ranging from 100° to 105°F., and lasting from a few days to several weeks. Respiratory manifestations such as cough or dyspnea may appear, but are usually related to accompanying respiratory tract infection.

The outstanding physical finding is a pericardian friction rub. This frequently appears with the onset of the disease or during the first day, in contract to myocardial infarction in which it is less widely distributed, and usually first detected several days after coronary artery closure has occurred. The average duration of the rub in "benign" pericarditis is about 7 to 9 days, although it may persist for from 1 day to 4 weeks, often disappearing for a short period and then reappearing Cardiac dysfunction is uncommon. Arrythmias are very infrequent; gallop rhythm has been described. Shock is rarely observed. Although pericardial effusion is not uncommon, signs of cardiac compression are usually of insufficient degree to warrant paracentesis. Dilatation of the heart may occur in some cases, but congestive failure is rare. Unlike most of the other etiologic types of pericardial infection, pleural effusion is a frequent finding in benign serofibrinous pericarditis The fluid is present either on the left or on both sides of the chest; it is very rarely detected only on the right.

The white blood count is usually elevated to between

etiology of the process may be suggested by the mode of onset, the course of the disease, and the presence or absence of associated conditions, it can be established definitely only by microscopic, chemical, and bacteriologic investigation of the pericardial fluid. This is one of the important reasons for carrying out a pericardial tap.

The treatment of acute infections of the pericardium depends on two factors. (1) The nature of the invading organism: this determines the necessity of using an antimicrobial agent and the drug to use if such therapy is indicated. (2) The development of signs of cardiac tamponade; when these appear, and especially if they are progressing, removal of fluid from the pericardial sac is imperative and life-saving in some cases. Repeated aspirations may be required in some instances; in others, a window must be made in the pericardium to allow constant drainage. It must be stressed that there are only 2 indications for pericardial tap; (1) to establish the etiology of the disease, and (2) to relieve pressure on the heart and great vessels. This procedure is attended by the risks of superimposed infection, hemorrhage, or trauma to a coronary artery which may be followed by myocardial infarction.

Acute Benign Serofibrinous ("Viral") Pericarditis

Acute benign serofibrinous ("viral") pericarditis is a relatively common disease observed most frequently in persons between 30 and 45 years of age, and in men more often than in women. It is usually preceded by an undefined respiratory tract infection which has been present for from 2 weeks to 2 months, or may follow "atypical viral pneumonia." Some cases accompany hypersensitivity reactions; pericarditis with effusion has been noted in serum sickness.

The onset of "viral" pericarditis is acute in 60 per cent of cases. The outstanding manifestation is pain which may

start abruptly and be quite severe, or be very mild in the beginning and become progressively worse. The discomfort is aggravated by breathing, coughing, swallowing, or rotation of the upper part of the trunk. It is substernal or precordial in location and may radiate to the interscapular area, neck, epigastrium, or the left arm when it is often confused with myocardial infarction. The duration of the pain is variable; it may be present for only several minutes or may persist as the most prominent feature of the disease for several weeks.

Fever is present in practically all cases, ranging from 100° to 105°F, and lasting from a few days to several weeks. Respiratory manifestations such as cough or dyspnea may appear, but are usually related to accompanying respiratory tract infection.

The outstanding physical finding is a pericardian friction rub. This frequently appears with the onset of the disease or during the first day, in contract to myocardial infarction in which it is less widely distributed, and usually first detected several days after coronary artery closure has occurred. The average duration of the rub in "benign" pericarditis is about 7 to 9 days, although it may persist for from 1 day to 4 weeks, often disappearing for a short period and then reappearing. Cardiac dysfunction is uncommon Arrythmias are very infrequent; gallop rhythm has been described. Shock is rarely observed. Although pericardial effusion is not uncommon, signs of cardiac compression are usually of insufficient degree to warrant paracentesis. Dilatation of the heart may occur in some cases, but congestive failure is rare. Unlike most of the other etiologic types of pericardial infection, pleural effusion is a frequent finding in benign serofibrinous pericarditis. The fluid is present either on the left or on both sides of the chest; it is very rarely detected only on the right.

The white blood count is usually elevated to between

15,000 and 20,000 per mm^3, although it may be as high as 50,000; there is a marked increase in neutrophiles with many young forms. The sedimentation rate is elevated in practically all cases. Very little information concerning the characteristics of the pericardial fluid is presently available. In the few cases in which it has been studied, it has been straw-colored or bloody and has contained cells, most of which were lymphocytes.

Roentgenographic study of the chest reveals enlargement of the cardiac silhouette in 80 per cent of patients. Rapid and repeated fluctuation in size may occur during the course of the disease; it has been suggested that this is due to dilatation of the heart rather than development and absorption of pericardial fluid. X-ray often reveals pulmonary infiltration or pleural effusion in those cases in which the pericarditis is associated with or follows a "viral" pneumonia. The electrocardiographic changes described above are frequently noted.

The duration of acute benign serofibrinous pericarditis is 2 to 12 weeks, the average being 7 weeks. It recurs in about 15 per cent of cases. One patient has been described in whom 4 recurrences were present, and the disease lasted for a full year. The prognosis for life and complete recovery is excellent. Chronic constrictive pericarditis is not a sequel.

Although most cases of acute benign pericarditis fail to respond to antibiotic agents, tetracycline compounds appear to be effective in some. It may be worthwhile to give tetracycline or chlortetracycline (Aureomycin) in a dose of 0.25 to 0.5 gm. orally every 6 hours when clinical manifestations are severe. Good results have also been reported following the administration of ACTH: the effectiveness of this type of therapy remains to be proved.

The following table summarizes the points of importance in the differential diagnosis of acute benign serofibrinous pericarditis and myocardial infarction (Table I).

TABLE I

Symptom or Sign	*Acute Benign Pericarditis*	*Myocardial Infarction*
Pain	Aggravated by motion or swallowing. Lasts for days to weeks.	Not affected by movement or swallowing. Short duration.
Friction rub	Present in 1-2 hours after onset of disease. Lasts for days to weeks.	Rarely appears before 24 hours. Lasts short time.
Shock	Rare	Common
Fever, Leucocytosis and Elevated Sedimentation Rate	Appear very early Common	Appear only 24-48 hours after onset.
Pleural Pain		Rare, unless pulmonary *infarct occurs*
Cardiac Arrythmia	*Very uncommon*	Common
Electrocardiographic changes	Elevated S-T followed by depression and inversion of T waves R waves present. No reciprocal changes	Deep Q and absent R waves. Reciprocal changes.
Fluoroscopic Study of Heart	Size of cardiac silhouette undergoes rapid changes.	Changes in heart size slow, if they occur.

Tuberculosis Pericarditis

About 7 to 10 per cent of all cases of pericarditis are caused by the tubercle bacillus. Tuberculosis of the pericardium occurs most often in individuals under 40 years of

age and is commonest in men and in Negroes. As a rule, it is secondary to tuberculous infection in another site in the body, but the manifestations resulting from pericardial involvement may be so outstanding that they mask the signs of other disease. These cases are called "primary" tuberculous pericarditis, careful study, however, usually reveals other sites of tuberculosis. Two mechanisms are responsible for the production of tuberculous pericarditis; (1) direct extension from caseous hilar or mediastinal lymph nodes, pleuritis, or, very rarely, myocardial tuberculoma, and (2) hematogenous dissemination from foci in the lungs, skeletal system, or urogenital tract.

The onset of tuberculous pericarditis is usually slow and insidious, and may be so overshadowed by the manifestations of tuberculosis in other sites that it is overlooked for some time. The appearance of large or rapidly accumulating ascites, dyspnea, edema, or precordial pain should suggest this disease. Pain is often mild and very rarely severe; it is occasionally absent or atypical in location and distribution. It has been suggested that patients with fever and unexplained cardiac complaints should be suspected of having tuberculous pericarditis.

The physical findings are similar to those present in other forms of pericardial infection. Friction rub is usually present and lasts from a few days to several weeks. Cardiac arrythmias, especially auricular fibrillation, occur more frequently than in acute benign serofibrinous pericarditis. The clinical course is variable. Fever may be low grade or spiking in character. Manifestations of compression of mediastinal structures and cardiac tamponade are not uncommon.

The white blood count is normal or elevated, with an increase in neutrophiles. The sedimentation rate is characteristically rapid. Electrocardiogram reveals the changes described above. Because pericardial effusion is common, x-ray of the chest usually shows an increase in size of the

cardiac silhouette. Pulmonary parenchymal lesions are d monstrable in many cases.

The diagnosis of tuberculous pericarditis is usually su pected on the basis of clinical findings but can be prov only by careful study of the pericardial fluid. For this reas it is necessary to perform *pericardial paracentesis* when th disease is thought to be present. The fluid is usually stra colored and contains erythrocytes; it may be grossly blooc The number of white blood cells is between 6,000 and 8,0 per mm^3; *lymphocytes are predominant. Tubercle baci* can be demonstrated in acid-fast stained smears, in cultur or inoculated guinea pigs. The sugar content of the peric dial fluid is usually reduced below the normal level. Biop *of the pericardium is very helpful in establishing t* diagnosis and should be carried out, if possible.

The prognosis in untreated tuberculous pericarditis is ve grave, the fatality rate being between 80 and 90 per ce Several factors are of importance in determining the o come. (1) *Age*—the older the patient, the poorer the o look; (2) *Number of bacteria detectable in the pericard fluid*—the greater the ease with which acid fast organis are demonstrable in stained smears, the less favorable t prognosis; (3) *Race*—Negroes have a poorer outlook f recovery than white persons, (4) *Degree of severity a location of tuberculous infection outside the pericardium.*

Caseation necrosis and an outpouring of fibrin are chara teristic of tuberculosis of the pericardium. Because of th the pericardial sac becomes obliterated by a thick, toug membrane which eventually calcifies and fuses the pari and visceral layers. As a result, constrictive pericarditis common and develops in treated as well as in untreat cases.

The chemotherapy of tuberculous pericarditis is the sa as that for pulmonary tuberculosis (Chapter VII). Progr *sive increase of pericardial effusion* with advancing degr

of cardiac tamponade is a common problem. Although relief is produced by repeated paracentesis in many cases, open drainage becomes necessary in some. Pericardiectomy may need to be carried out in the acute stage of the disease if all other measures fail. The presence of fever and other signs of active infection do not contraindicate this procedure when compression of the heart and great vessels threatens life, or when edema, ascites, hepatomegaly, or the superior vena cava syndrome (see above) develop and progress. Delay in removal of the constricting pericardium may lead to myocardial damage which may be responsible for dilatation of the heart and acute cardiac failure after operation.

Suppurative (Pyogenic) Pericarditis

Suppurative pericarditis is produced most frequently by *Staph. aureus*, the pneumococcus, or beta-hemolytic streptococcus; the meningococcus and *P. tularensis* may also be responsible. The process is characterized by an acute inflammatory reaction with an outpouring of neutrophiles and fibrin. The surface of the pericardium has a shaggy appearance. Organisms reach the pericardium by one of three routes: (1) extension from infections of the lung, pleura or mediastinum, (2) by way of the blood stream during bacteremia, or (3) by direct penetration following wounds, rupture of the esophagus or bronchus, or perforation of subphrenic or liver abscesses through the diaphragm. Suppurative pericarditis may be secondary to pneumonia (with or without empyema), osteomyelitis, acute bacterial endocarditis, puerperal sepsis, genitourinary infections, or any type of bacteremia. Most cases follow severe pneumococcal pneumonitis with bacteremia, especially if treatment is not given or is instituted late in the disease.

Since suppurative pericarditis usually complicates other infections, it is very often difficult to detect, because it is

overshadowed by the primary process. The appearance of a friction rub is frequently the first indication that the pericardium is involved. This emphasizes the importance of daily examination of the heart in all cases of severe bacterial infection, especially if bacteremia is present. If the primary process in a serious infection does not account adequately for persistent signs of sepsis, or if unexplained dyspnea, cyanosis, increased venous pressure, or progressive cardiac tamponade develop, the possibility of acute pericarditis must be considered.

The diagnosis of suppurative pericarditis is made on the basis of the physical and x-ray findings described above and the demonstration of bacteria in a pericardial fluid which has the characteristics of an exudate. The temperature is usually high, often "spiking". There is high grade peripheral leucocytosis with a marked increase in neutrophiles, many of which are young forms. The pericardial effusion is usually purulent and contains a large number of cells, most of which are neutrophiles, it may be bloody. The quantity of sugar is reduced. Gram-stained smears of the fluid usually reveal bacteria. Cultures on appropriate media must be carried out, whenever possible. This is the only means by which the causative organisms can be identified and made available for testing of sensitivity to various antimicrobial drugs.

The treatment of suppurative pericarditis depends entirely on the nature of the responsible agents. If *Staph. aureus* is the cause, the intramuscular administration of 1,000,000 units of crystalline benzyl (aqueous) penicillin G every 4 hours is indicated. If response to this drug is not adequate, chloramphenicol plus erythromycin (0.5 gm. of each intramuscularly every 6 hours per day) should be substituted. The organisms must be examined for susceptibility to a number of antibiotics; the results of such tests are very important in selection of the most effective drug. Penicillin is

the agent of choice in the management of pneumococcal and beta-hemolytic streptococcal pericarditis; the dose is the same as for staphylococcal infection. Therapy should be continued for a minimum of 2 weeks. When other organisms are involved, the agents to which they are most sensitive are administered in large doses. Surgical treatment is not necessary when chemotherapy is undertaken early and the clinical response is good. If, however, the disease has been present for some time, the pericardial exudate is very thick, or there is evidence of increasing cardiac tamponade, incision of the pericardium and open drainage is often necessary; it has been recommended that the antibiotic agent being used be applied to the pericardial surface in such cases.

The prognosis is grave in untreated suppurative pericarditis. If the disease is not detected and treated, death is the usual outcome. In patients who recover, constrictive pericarditis may develop despite the use of antimicrobial agents. Calcification of the pericardium may occur, but is much less common than with tuberculous infection.

Myocarditis

Myocarditis develops in the course of some infectious diseases. It may be due to (1) direct invasion of the myocardium by bacteria or viruses, (2) the action of various bacterial products and "toxins" which produce physiologic and anatomical disturbances, or (3) allergic reactions. The etiology of some types is unknown. There are usually no symptoms or clinical signs indicating myocardial involvement, although precordial or substernal pain or cardiac failure may appear. In most instances, myocarditis is not suspected unless electrocardiograms are taken or it is detected at autopsy. It may cause death in diseases which are usually not fatal. It often develops at a time when the primary disease seems to be progressing favorably.

Staph. aureus, the beta-hemolytic streptococcus, the pneumococcus, and *Streptobacillus moniliformis* may invade the myocardium during the course of bacteremia and produce multiple abscesses. Although electrocardiographic abnormalities can be detected in such cases, the presence of the lesions is usually not suspected until necropsy reveals them. Myocarditis may be due to direct invasion by viruses. This is observed occasionally in poliomyelitis and influenza in which clinical manifestations, electrocardiographic abnormalities, and anatomic changes have been described and the causative agents isolated from the myocardium, a rare death in these diseases can be attributed to the myocardial involvement. Myocarditis is frequent in scrub typhus, a rickettsial infection. It also occurs in trichinosis and may be responsible for a fatal outcome; the larvae can be demonstrated in the cardiac muscle. Invasion of the myocardium by the spirochetes of syphilis has been described.

Toxic products of bacteria may be responsible for severe myocarditis. An outstanding example of this is diphtheria, in which electrocardiographic abnormalities can be detected in about 65 per cent of patients; myocardial involvement is often severe and is a common cause of death in this disease (Chapter VI). Fatal necrotizing myocarditis, distinct from rheumatic fever, has been described following streptococcal pharyngitis

Electrocardiographic abnormalities have been noted in cases of serum sickness following the administration of horse serum or penicillin.

Myocarditis, the exact mechanism of which is not evident, has been described in a large number of infections. It has been noted in mumps; both electrocardiographic changes and clinical abnormalities (persistent heart block) may be present. Necrosis of cardiac muscle has been observed in Coxsackie virus disease. About 15 per cent of patients with measles have ECG tracings suggestive of active myocardial disease; complete heart block with Stokes-Adams attacks

ıas been reported in one case. Anatomic evidence of severe nyocarditis has been discovered at autopsy in individuals lying of influenza and psittacosis. Electrocardiographic abıormalities appear in infectious mononucleosis, chicken pox, ubella, and "atypical viral pneumonia". Whether these are lue to direct invasion of the infectious agents or are proluced by some other mechanism, possibly hypersensitivity, s not known.

Various ECG changes have been described; all may occur, n varying combination, in different infections and none is pecific for a particular disease. The abnormalities which ıave been reported include depression or inversion of T vaves, elevation or lowering of S-T segments, increase in ᐩ-R and Q-T intervals, partial and complete heart block, undle branch block, and alterations in direction and conguration of P waves. The mere demonstration of an abıormal tracing is probably insufficient evidence on which to ase a diagnosis of myocarditis. Fever, tachycardia, electrote imbalance, and probably other physiologic disturbances ıay produce the same kinds of ECG changes. Clinical-anatomical—electrocardiographic correlation is necessary beore the significance of an altered ECG in relation to the ctual presence of myocarditis in many infectious diseases ın be established.

There is no treatment for myocarditis except in the rare ıstances in which it is due to direct bacterial invasion; the resence of this type of disease cannot be detected clinally. When heart failure occurs or potentially dangerous rythmias appear, the advisability of treatment is raised. igitalis is of questionable value; many cardiologists feel ıat it is definitely contraindicated. A number of cases have een treated with this drug, however, and good results ave been reported. When digitalis is not given, restriction salt and the administration of diuretics may be very efctive in relieving the manifestations of cardiac decompenıtion. Quinidine has been used in patients exhibiting au-

ricular arrythmias in the course of infectious diseases. The value of this drug in these situations has not been proved; it is not beneficial in diphtheritic myocarditis. Procaine amide (Pronestyl) may be tried when ventricular disturbances appear; experience with the use of this agent in infections is too limited to allow any conclusions.

Subacute Bacterial Endocarditis

Subacute bacterial endocarditis, the commonest form of cardiac infection, is usually secondary to rheumatic heart disease, congenital cardiac lesions, myocardial infarction, or chronic debilitating diseases in which platelet thrombi develop on heart valves. It occurs most commonly in patients 21 to 30 years of age, next most frequently in those 31 to 40 years old, and less often in individuals 11 to 20 years of age. It may appear at any age, however, and has been observed in the seventh decade of life. The commonest predisposing acquired valvular defect is aortic regurgitation; second in *frequency is aortic regurgitation together with mitral insufficiency*, third, mitral insufficiency alone, and fourth, tricuspid insufficiency. Subacute bacterial endocarditis develops very infrequently in cases of fully developed ("tight") mitral stenosis.

Bicuspid aortic valve is the congenital cardiac lesion associated most often with subacute bacterial endocarditis. Next in frequency are patent ductus arteriosus and coarctation of the aorta. Subaortic stenosis, patent interventricular septal defect, and pulmonic stenosis may also predispose to the development of this disease.

Very rarely, the thrombus formed over the infarcted area of cardiac muscle after coronary occlusion is invaded by bacteria and endocarditis appears. In people with arteriosclerosis and other chronic disorders, sterile platelet-fibrin thrombi may develop on the heart valves and become infected.

Four factors are involved in the pathogenesis of subacute

bacterial endocarditis: (1) *A damaged heart valve*, (2) *Sterile platelet thrombi*. Eddy currents in the blood stream produced by a distorted valve are responsible for the deposition of platelets and fibrin and formation of thrombi on the damaged valve. (3) *Bacteremia*. Transient transport of bacteria in the blood probably occurs periodically in many normal persons. Tonsillectomy, abdominal operations, prostatectomy, and dental extraction (20 to 60 per cent) may be followed by bacteremia of short duration. In persons with normal hearts, this is of no consequence. When sterile thrombi are present on damaged valves, however, the organisms may settle out in the involved area, multiply, and produce disease. About 25 per cent of cases of subacute bacterial endocarditis are secondary to dental extractions. (4) *An elevated antibody titer for Strep. viridans*. A high level of agglutinin allows clumps of bacteria rather than single cells or chains to be deposited. This provides an inoculum large enough to permit growth of the organisms and the production of infection.

The right side of the heart is involved in about 10 per cent of patients with subacute bacterial endocarditis. The lesions which predispose to this type of disease most frequently are tricuspid insufficiency and interventricular septal defect.

A variety of bacteria may be responsible for subacute bacterial endocarditis. However, over 90 per cent of the cases are due to alpha streptococci or *Strep. viridans*. Group D streptococci, naturally resistant to both penicillin and streptomycin, are an important and increasingly frequent cause of the disease; the organisms may be alpha, beta, or non-hemolytic. Non-pathogenic *Neisseria*, gonococci, meningococci, *Staph. albus* and other organisms have been involved in some cases.

The clinical manifestations of subacute bacterial endocarditis are of 3 types; all are present in most cases. (1)

Symptoms and signs associated with infection. (2) Cardiac disorders. (3) Embolic and vascular phenomena.

The onset of subacute bacterial endocarditis is most often insidious and suggestive of low-grade infection. Lassitude, weakness, anorexia, slight to moderate fever, and progressive anemia may persist for weeks or months before a patient seeks medical advice or the physician suspects the true nature of the disorder. The temperature elevation may be sustained at a low level or be intermittent or remittent in character; it may resemble tertian malaria. Although chills are not always present with the inception of the disease, they usually occur at some point in its course. The onset may occasionally be sudden and featured by high fever, shaking chills, generalized muscle and bone aching, loss of weight, and rapidly progressing hypochromic microcytic anemia which is usually due to the infection, but may be secondary to an acute hemolytic process. Diagnoses of tuberculosis, malaria, lymphoma, leukemia, "grippe", "viral" pneumonia, disseminated lupus erythematosus, thyrotoxicosis, typhoid fever, or renal, nervous system, or gastrointestinal disorders are frequently made. Persistent manifestations of infection in patients with congenital or acquired heart disease must always arouse suspicion of the possibility of subacute bacterial endocarditis. The disease occurs only rarely in cases of rheumatic heart disease in which auricular fibrillation or cardiac decompensation have developed; it is even more infrequent in instances in which both have appeared.

Embolization, aneurysm formation, and arteritis are features in many cases of subacute bacterial endocarditis. Small segments of the valvular vegetation may break off and be carried to any part of the body. Sudden blindness follows occlusion of the central artery of the retina. Renal and splenic infarcts are common. Hemiplegia and other localizing neurological signs follow obstruction of cerebral vessels.

Emboli are also responsible for petechiae in the skin and mucous membranes and for subungual hemorrhages in the fingers and toes.

It has been suggested that some of the vascular phenomena occurring in subacute bacterial endocarditis may be due to an arteritis. Study of the arterial bed in the area of some lesions has revealed a chronic inflammatory reaction in the walls of the arteries and arterioles, without evidence of embolic occlusion. This is thought to be the mechanism of production of Osler's nodes. These lesions appear in about 50 per cent of cases. They consist of red tender spots in the soft tissue of the terminal phalanges of the hands and tend to occur in crops involving different fingers, usually in groups of three or four. Janeway lesions are also thought to be due to arteritis. These appear primarily on the palms and soles, and are irregular, erythematous, sometimes partially hemorrhagic, and not tender, a point which differentiates them from Osler's nodes. Boat-shaped retinal hemorrhages (Roth spots) are infrequent; they are probably related to arteriolar inflammation.

Mycotic aneurysms may develop in some blood vessels in the course of subacute bacterial endocarditis. These are the result of invasion of the vascular wall by bacteria brought to the site in a small embolus. The elastic membrane of the vessel is destroyed and aneurysmal dilatation and persistent infection develop. The presence of this lesion is usually not suspected until rupture and hemorrhage take place. Death may result from exsanguination.

Variation in the intensity and character of cardiac murmurs is said to be characteristic of subacute bacterial endocarditis. This is due to the changes produced by destruction and repair of the involved valve or to fluctuation in degree of heart failure and is absent in many cases; it may be observed more frequently in the early stages of acute rheumatic carditis. Rupture of the infected heart valve may take place and lead to the appearance of a loud "cooing" or "sea-

gull" murmur. Cardiac arrythmias develop uncommonly despite the frequent presence of myocarditis as demonstrated by interstitial collection of small round cells (Bracht-Wachter bodies); prolonged conduction time is detected most often. Auricular fibrillation may appear late in the course of the disease. Precordial or substernal pain occurs occasionally and results from myocarditis or embolic occlusion of a coronary artery; in some instances, there is no explanation for it. Cardiac failure is not common but, when present, is usually a late feature; it may develop with great rapidity after rupture of the infected valve.

Enlargement of the spleen is found at autopsy in all cases of subacute bacterial endocarditis, although it is detected in only 80 to 90 per cent during life. Pain in the left upper quadrant of the abdomen, often radiating to the shoulder and accompanied by a friction rub, usually follows splenic infarction. Clubbing of the fingers is common The kidney is very frequently involved. Multiple emboli may produce focal embolic glomerulitis Either acute or chronic glomerulonephritis may develop; the latter often appears without a detectable acute phase. Hematuria, albuminuria, cylindruria, azotemia, and progressive renal failure are noted in about one-third of all patients. Both chronic glomerulonephritis and embolic glomerulitis are present simultaneously in most of these cases. Large renal infarcts produce severe flank pain, costovertebral angle tenderness, increase in fever, leucocytosis, and gross hematuria. The lungs are usually not affected. However, multiple pulmonary infarcts are characteristic of endocarditis involving the right side of the heart. Infarction of the gastrointestinal tract or liver is rare because of the nature of the blood supply. With progressive occlusion of the hepatic vein, however, the liver may become infarcted. Anorexia, post prandial distress, and abdominal pain are common; they are usually not related to cardiac involvement, although they may be exaggerated when congestive failure takes place. Jaundice develops oc-

casionally; it is observed most often late in the course of right sided endocarditis and is probably due to cardiac decompensation and hepatic congestion. The brain or spinal cord may be seriously involved. Repeated embolization produces focal embolic encephalitis which is often difficut to differentiate from other types of localized or diffuse cerebral disease. Despite the fact that the emboli contain organisms, infections are uncommon, and brain abscess or purulent meningitis develops only rarely. Arthralgia is very common and usually transitory. Marked swelling and redness of the joints is rare; differentiation from acute rheumatic fever which is sometimes present at the same time may be very difficult. Tenderness over bones, especially the lower end of the sternum, is a frequent finding.

The bacteria-free stage of subacute bacterial endocarditis develops in some untreated patients and a few who have received antimicrobial agents; in the former, it is related to a high level of circulating antibody. These individuals have active valvular infection, but organisms cannot be isolated from the peripheral circulation. In one group of untreated cases, 20 per cent had negative blood cultures. In this syndrome, fever is either of low degree or absent. The outstanding manifestations are repeated emboli, urine abnormalities consistent with chronic glomerulonephritis, progressive renal failure, cafe-au-lait discoloration of the skin, hepatomegaly and jaundice. Death occurs in about 35 to 40 per cent of these patients and is usually due to "uremia".

The right side of the heart is involved in about 10 per cent of cases of subacute bacterial endocarditis. When interventricular septal defect is the predisposing lesion, the infected vegetations are present on the right wall of the septum around the opening, or at the point on the wall of the right ventricle at which the jet of blood impinges as it is forced through the defect during systole. Although blood cultures are usually negative, organisms pass the pulmonary filter in some patients and can be recovered from the peri-

pheral circulation. The characteristic manifestations of righ sided endocarditis are chest pain due to repeated pulmona infarcts which are often mistaken for episodes of pne monia, laboratory and clinical findings of acute or chron glomerulonephritis, hepatomegaly, and jaundice. It has be suggested that the appearance of progressive renal failu in an individual with chronic heart disease and fever sufficient basis for suspecting the presence of infection the right-side of the heart.

The blood picture in subacute bacterial endocarditis not diagnostic. The white blood count is normal, elevated high levels, or decreased. A varying number of plasma ce may be present in the peripheral circulation; they are oft numerous in the bone marrow. It has recently been report that blood obtained from the *ear lobe* contains a large nu ber of histiocytes and that this finding is of diagnostic si nificance. Hypochromic, microcytic anemia is present almost all cases. Acute hemolysis, with a positive Coom test, is encountered occasionally. The urine is normal some instances; in others, it has all of the abnormaliti characteristic of acute or chronic glomerulonephritis. La oratory evidence of hepatocellular dysfunction is detect when jaundice and hepatomegaly are present. Hypoalb minemia and hypergammaglobulinemia are frequent w prolonged infection. Electrolyte imbalance and azotemia a noted in patients with progressive renal failure. The m important laboratory procedure in subacute bacterial enc carditis is culture of the blood. The optimal time to ca this out is the point at which the temperature begins rise or during a shaking chill, cultures obtained at the heig of the fever may be negative. At least 5 blood cultu should be made in each case and they should be incubat under CO_2 for at least 14 days before being discard There is no advantage in culturing arterial blood. Wh the organisms have been isolated, they must be test promptly for sensitivity to various antibiotic agents.

The diagnosis of subacute bacterial endocarditis is suspected clinically in patients with acquired or congenital heart disease who develop manifestations of infection and have embolic phenomena. Isolation of bacteria from the blood confirms it. The disease is most often overlooked when only low-grade fever and general malaise which are common manifestations in the early phase are present. Such cases are often considered to have "grippe" or a "virus infection". The only way in which the frequency of early diagnosis can be increased is by adopting the practice of carrying out blood cultures in all persons with known cardiac abnormalities who have fever of undetermined origin which persists for more than a few days. The physician must have a high index of suspicion for this disease.

The course of untreated subacute bacterial endocarditis is practically always downhill. The fatality rate is 97 per cent; some patients may live as long as 3 to 4 years. Repeated embolic phenomena, progressive anemia, fever interspersed with chills, anorexia, loss of weight, cardiac arrythmias, congestive heart failure, hepatomegaly, splenomegaly, jaundice, renal decompensation, and central nervous system involvement with blindness, hemiplegia, or encephalitis characterize the natural history of the disease in the fatal case; all of these do not appear in every case. The causes of death are (1) uncontrolled infection, (2) deposition of an embolus in a vital area such as the brain or one of the coronary arteries, (3) heart failure, (4) renal insufficiency, (5) rupture of a mycotic aneurysm, and (6) intercurrent bacterial infections.

The outlook for recovery in subacute bacterial endocarditis has been tremendously improved by chemotherapy. It must be stressed, however, that it is not necessary to initiate the treatment at the moment the presence of the disease is first suspected. Since infection of the heart valve has been present in most cases for 2 or more months before patients come to the attention of a physician, a delay of 2 to 3 days

for the purpose of obtaining an adequate number of blood cultures and identifying the causative organism rebounds to the benefit rather than the harm of the individual. If death occurs within a few days, it is usually not due to untreated infection but to such complications as embolization to a vital area or cardiac failure, neither of which is prevented by antibiotic agents. Once a sufficient number of blood cultures have been made, therapy may be started in instances in which the manifestations are severe, especially if the clinical findings are characteristic. In some patients, it is impossible to obtain a positive blood culture regardless of the number of attempts made and the media used; this is the case when high levels of circulating antibody are present or the infection involves the right side of the heart. In these, therapy must be initiated on the basis of a suggestive syndrome. Although treatment is undertaken unnecessarily in some instances on this basis, it is clinically sound practice to err on the side of treating because of the very high death rate in the untreated disease. To delay until the picture is so fully developed that the diagnosis is obvious, may be to withhold therapy until it has little, if any, chance, to be effective.

The choice of antibiotic in subacute bacterial endocarditis depends on the nature and sensitivity of the responsible bacteria. Since the bulk of cases is due to *Strep. viridans*, most strains of which are sensitive to penicillin, this drug should always be included in the initial therapy. Group D streptococci are insensitive to penicillin or streptomycin alone, but are very susceptible to a combination of the two drugs Since some cases may be due to this organism, the writer has adopted the following procedure: Until the causative agent is recovered or, if isolated, has been tested for sensitivity to various antibiotics, 1,000,000 units of crystalline benzyl penicillin G plus 0.25 gm. of streptomycin are injected intramuscularly every 4 hours. If the bacteria are found to be highly susceptible to penicillin alone, strep-

tomycin is omitted. Partial insensitivity to penicillin does not eliminate the possibility of using this antibiotic effectively. In such instances, high blood levels of drug may be produced by increasing the dose to 10,000,000 or even 20,000,000 units per day. The administration of probenecid (Benemid) (0.5 gm. four times per day) aids in maintaining large quantities of penicillin in the blood by blocking renal tubular excretion.

Recent studies have suggested that the oral administration of 1,000,000 units of penicillin V every 3 hours for 4 weeks cures some cases of subacute bacterial endocarditis. This procedure should be undertaken with the understanding that it is still experimental and may fail to produce the desired results. Another method of treatment which has been employed has been the injection of crystalline penicillin G (500,000 units every 3 or 4 hours) for 2 weeks followed by oral administration of the drug in a dose of 1,000,000 units every 3 or 4 hours for the next 4 weeks. The writer is inclined to avoid oral therapy in this disease.

In cases in which the causative organisms are not sensitive to penicillin, the drug to which they are most susceptible must be given in large quantities. The tetracycline compounds (Aureomycin, Terramycin, Achromycin), chloramphenicol, bacitracin, and erythromycin have been used with good results in such instances.

The duration of treatment of subacute bacterial endocarditis is of great importance in determining the outcome. It must be kept in mind that destruction and healing are usually proceeding simultaneously in the valvular lesion. Effective chemotherapy, by suppressing bacterial multiplication, alters the situation so that the process of repair becomes predominant and cure finally occurs. This may require a considerable period of time. Treatment for only 2 weeks has been reported to be successful in some cases. The writer has had no experience with such abbreviated therapy but feels that it cannot be recommended as the

usual regimen. It is safest to continue administration of the antibiotic which is selected for at least 4 to 6 weeks depending on the severity of the disease and the type and sensitivity of the causative organism. Relapses should be restudied bacteriologically and treated with the appropriate antimicrobial agent for another period of 4 to 6 weeks.

Not all treated cases of subacute bacterial endocarditis survive. In some instances, death occurs because therapy has been initiated too late and is due to the uncontrolled infectious process. In others, despite eradication of the bacteria, heart failure, cerebral infarction, embolic occlusion of one of the coronary arteries, or renal failure may produce a fatal outcome even weeks or months after full recovery is considered to have occurred. Treatment has reduced the mortality rate to between 10 and 15 per cent. The possibility of recurrence exists in every "cured" case and is unpredictable; it may be due to the organism responsible for the initial episode or to a different one. Patients with as many as 3 episodes of subacute bacterial endocarditis have finally recovered when retreated with effective drugs.

Acute Bacterial Endocarditis

There are three essential differences between subacute and acute bacterial endocarditis; (1) the causative organisms, (2) the destructive character of the valvular lesion in which there is no evidence of a tendency to heal, and (3) the frequency with which normal cardiac valves are involved. The bacteria most often responsible for acute bacterial endocarditis are *Staph. aureus*, *H. influenzae*, the beta-hemolytic (group A) streptococcus, pneumococcus, meningococcus, and gonococcus. The infection progresses rapidly and produces ulceration and destruction of the involved leaflets which are prone to rupture. About 60 per cent of patients have no underlying cardiac disorder. The diseases which predispose to acute infection of the heart

valves include furunculosis, pneumonia, meningitis, gonorrhea, and infected wounds. The organisms are deposited on the heart valves in the course of the bacteremia which may develop during any of these infections. The aortic valve is involved most often.

Signs of illness usually develop rapidly in acute endocarditis. High fever, shaking chills, rapidly progressive anemia, and embolic phenomena appear very soon after infection of the heart valve has occurred. The picture is more severe than is observed in the subacute type of disease. Cardiac murmurs appear early and often change with greater rapidity; they are usually systolic and may be very soft or *rarely completely absent. Splenomegaly is common.* Clubbing of the fingers is present less frequently than in subacute endocarditis because, without treatment, patients do not live long enough for this manifestation to develop. Heart failure and a variety of arrythmias may occur early. Rupture of the aortic valve is not infrequent and is accompanied by the appearance of a high-pitched "cooing" or "sea-gull" murmur or a diastolic murmur and peripheral signs of aortic insufficiency; it is usually followed, within a few days, by acute cardiac failure. The right side of the heart, mainly the tricuspid valve, is involved uncommonly. Although *Staph. aureus* and *H. influenzae* may produce this type of disease, it is thought to be most frequent with gonococcal infection.

The possibility of acute bacterial endocarditis should be suspected in any individual who, during or after one of the predisposing diseases listed above, develops high fever or responds poorly to treatment. The appearance of a murmur in a previously normal heart is very suggestive. Embolic phenomena, rapidly changing cardiac murmurs, or the early development of heart failure are important and helpful clinical signs. Proof of the presence of the disease is established by the demonstration of bacteremia.

The prognosis of acute bacterial endocarditis without

treatment is hopeless. The disease is so fulminating in most cases that only 2 to 3 weeks or less may elapse between onset of symptoms and death. In many instances, the fatal outcome results from overwhelming infection; in others, it is due to rupture of the aortic valve and the appearance of intractable cardiac failure, deposition of an embolus in a vital area, or rupture of a mycotic aneurysm. Effective therapy may convert acute endocarditis to the subacute variety by retarding the rate of progression of the disease; the risk of fatal emboli or cardiac failure is still high, however.

The treatment of acute bacterial endocarditis is entirely dependent on the nature of the causative organism. Therapy must be initiated as soon as possible because of the rapidity *with which the infection progresses. After a sufficient number* of blood cultures have been obtained (usually in 8 to 12 hours), therapy should be started with the assumption that *Staph. aureus* is involved. Treatment must not be withheld longer than 24 hours in severely ill cases. Aqueous penicillin is the drug of choice in patients who have developed the disease outside the hospital and have not been treated with this drug for the predisposing illness. The dose is 1,000,000 units intramuscularly every 4 hours. If there is a possibility that a penicillin-resistant organism is responsible, chloramphenicol plus erythromycin (0.5 gm. of each intramuscularly every 6 hours) should be substituted. As soon as the organism has been isolated from the blood, it must be examined for sensitivity to various antimicrobial agents and therapy altered on the basis of the results of the tests. Treatment must be continued for a minimum of 4 weeks; 6 weeks is preferred in some clinics. Some cases are unfortunately due to staphylococci which are insensitive to all antibiotics.

The prognosis of acute bacterial endocarditis has been improved by chemotherapy when some types of bacteria (*H. influenzae*, the beta-hemolytic streptococcus, gonococcus, and meningococcus) are the causative agents. When

Staph. aureus is the responsible organism, the outcome is very unpredictable. Although fatality rates in staphylococcal endocarditis have been reduced to 40 to 50 per cent in some hospitals, in others it is practically as high as it was in the pre-antibiotic era because of the frequency with which drug-resistant strains are involved. The rapid progression of valvular destruction, the tendency to metastatic abscess formation, the frequency and rapidity of onset of cardiac failure, and the high risk of embolization to vital areas make the outlook for recovery guarded even when chemotherapy appears to be effective.

INFECTIONS OF BLOOD VESSELS

Thrombophlebitis

Thrombophlebitis is a common disease. Although it often presents with the manifestations of infection such as fever, chills, and leucocytosis, and may accompany a number of specific infectious diseases, its exact etiology is not clear in many instances. Since inflammation of veins occurs in a large number of conditions which are not infectious in origin, it is very doubtful that it is due to direct invasion of the vein wall by infectious agents in most cases. Scarlet fever, influenza, meningitis, varicella, variola, bacillary dysentery, brucellosis, erysipelas, pyelonephritis, tuberculosis, pneumonia, cellulitis, syphilis, typhoid fever, cholera and typhus may be accompanied by thrombophlebitis. It is also observed in neoplasms (lung, pancreas, colon, stomach, uterus, and ovary), metabolic diseases (gout, diabetes mellitus, and hyperthyroidism), cardiovascular disorders (hypertension, congestive failure, thromboangiitis obliterans, and Raynaud's syndrome), hematologic diseases (polycythemia vera, thrombocythemia, hyperfibrinogenemia, and megakaryocytic aleukemic myelosis), trauma, allergic reactions, and as an isolated lesion. One form of thrombophlebitis is migrating in character (thrombophle-

bitis migrans), its etiology is unknown. Other than the administration of anticoagulants and venous ligation, there is no therapy.

One type of acute thrombophlebitis is due to bacterial invasion of the vein wall. It usually follows insertion of plastic catheters into veins for the purpose of administering fluids and is most frequent when the tube is allowed to remain in place for several days or longer. Thrombi are formed and are invaded by *Staph. aureus*. Severe illness may develop. Fever, chills, reddening of the skin over the involved vein which becomes hard and cord-like, local pain and tenderness, and bacteremia are often present. Treatment consists of removal of the catheter and the administration of anticoagulant drugs and penicillin or another antibiotic to which the organism is sensitive.

Infected Arteriovenous Aneurysms and Bacterial Endarteritis

Thrombi present in arteriovenous aneurysms in the extremities may be invaded by *Strep. viridans* and other organisms. Thrombosis and infection of arteries may also occur; the best example of this is endarteritis of a patent ductus arteriosus. One case in which the pulmonary artery was involved has been described.

The clinical manifestations of subacute endarteritis are often difficult to differentiate from those of bacterial endocarditis. Signs and symptoms of infection (fever, chills, malaise, leucocytosis), cardiac murmurs, and embolic phenomena occur with bacterial invasion of arterial walls and are identical with those present when heart valves are infected. It should be emphasized that cardiac murmurs may be present in the absence of heart disease in cases of arteriovenous aneurysm. Blood cultures are often positive.

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CHAPTER IX

INFECTIONS OF THE PERITONEUM AND INTESTINAL TRACT

PERITONITIS

Infections of the peritoneum are common. They occur frequently (a) after leakage of organisms from the bowel, as in rupture of acute appendicitis, (b) following spread of bacteria from other organs in the peritoneal cavity, or (c) as a result of hematogenous dissemination from infectious processes outside the abdomen. Peritonitis may be classified on the basis of its pathogenesis into primary and secondary types: the former results from blood stream invasion by bacteria from extra-abdominal foci (most often the pneumococcus or beta-hemolytic streptococcus), while the latter follows contamination by organisms from the intestinal tract as a result of disruption of its continuity.

A variety of organisms may produce peritonitis. Beta-hemolytic streptococcal infection may be primary or follow upper respiratory tract infections, measles, erysipelas, scarlet fever, empyema, or lipoid nephrosis. Invasion by the pneumococcus occurs during pneumonia or in patients with lipoid nephrosis. In young girls, this organism frequently invades from the genital tract. Chronic or acute gonococcal salpingitis may be complicated by generalized or localized peritonitis. Tuberculous peritonitis, although now rare, may

acute bacterial endocarditis. Therapy is based on the nature of the causative organism and its sensitivity to various antibiotics. The agent found to be most effective *in vitro* should be administered in large doses for a minimum of 4 weeks. Surgical extirpation of the infected arteriovenous aneurysm or ligation of the patent ductus arteriosus should be carried out after the infection has been brought under control and while the patient is still receiving antimicrobial agents.

phrenic space, in the pelvis, in the lumbar gutter close to the spine, about the cecum, lateral to the sigmoid, or between loops of bowel. A localized form of peritonitis, perihepatitis, may follow gonococcal infection, this is the Curtis-Fitzhugh syndrome.

Intra-abdominal abscesses are usually very difficult to suspect unless a patient has an intestinal disorder known to predispose to peritonitis. The clinical manifestations of many of these lesions suggest only that infection is present, since localizing signs are often absent. With peri-appendiceal abscess, fever, leucocytosis, pain and tenderness in the right lower quadrant, and detection of an increasing mass on the right side by rectal examination are the characteristic signs and symptoms. Subphrenic abscess may be due to ruptured appendix, generalized peritonitis, infections of the liver or kidneys, or lymphogenous or hematogenous dissemination of bacteria. The majority of cases are observed after perforation of the stomach, duodenum, or appendix, or as a complication of liver abscess. Subphrenic abscess is characterized *mainly by the general manifestations which accompany any* bacterial infection, localizing signs are usually not detected by physical examination. The diagnostic features of this disease are elevation and immobility of the diaphragm on the side of the lesion (usually the right) demonstrable by fluoroscopic study. In some instances, particularly those in which gas-producing organisms are involved, a collection of gas is observed under the diaphragm.

The diagnosis of generalized peritonitis is usually not difficult. A history of the presence of a predisposing lesion followed by the signs, symptoms, and laboratory findings of bacterial infection plus manifestations of irritation of the peritoneum (pain, tenderness, spasm) and, in some cases, paralytic ileus (abdominal distension and absence of peristaltic sounds) are sufficient to establish the presence of the disease. The localized forms are more difficult to detect and,

result from infection of intra-abdominal organs during the course of miliary spread.

Generalized peritonitis is most common after spontaneous or accidental perforation of the intestines. The two lesions with which it is most often associated are rupture of a peptic ulcer or an inflamed or obstructed appendix. In these cases, infection of the peritoneum is not produced by any one organism but results from the simultaneous activity of the different bacteria normally present in the bowel.

Pain is one of the outstanding manifestations of peritonitis. The discomfort is poorly localized when only the visceral peritoneum is involved. When the parietal portion is affected, the pain increases in severity, may be excruciating, and is exaggerated by any movement of the body; the patient prefers to lie quietly with his legs drawn up. As paralytic ileus develops, the abdominal pain frequently decreases in intensity. Tenderness to palpation is generalized, marked, and, in the early stages, usually maximal over the area of the involved organ. Rebound tenderness is characteristic. When peritonitis is diffuse, the muscles of the abdominal wall are in spasm or are completely rigid; this often decreases as the course of the disease progresses. Distension appears and increases with the developing ileus, while peristaltic sounds diminish or disappear completely. Nausea and vomiting are frequent. Fever is always present, unless shock supervenes, and may be of varying degree and intermittent, remittent, or sustained. The pulse rate is usually rapid, often out of proportion to the height of the temperature. The white blood count is usually elevated, often to very high levels, and there is a marked increase in neutrophiles, many of which are young forms.

Localized peritonitis usually follows rupture of the intestime as a result of appendicitis, diverticulitis, etc. Abscess formation may complicate generalized peritonitis; this occurs most often in the area of a perforated appendix in the sub-

phrenic space, in the pelvis, in the lumbar gutter close to the spine, about the cecum, lateral to the sigmoid, or between loops of bowel. A localized form of peritonitis, perihepatitis, may follow gonococcal infection; this is the Curtis-Fitzhugh syndrome.

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when present in certain sites, produce the syndrome of "obscure" fever for weeks. They are frequently not detected until exploratory laparotomy is carried out. The diagnostic features of peri-appendiceal and subphrenic abscesses have been described above.

The treatment of peritonitis combines both medical and surgical approaches. Whether or not "conservative" therapy without surgical intervention is used is a matter for the surgeon to decide. In general, peritonitis secondary to leakage from the bowel cannot be eliminated until the area of bowel perforation has been closed. Some physicians prefer to treat such cases with appropriate antibiotics, upright position in bed, a Miller-Abbott tube, and intravenous fluids up to a week or more before surgical treatment is applied. In many clinics, operation is performed early and as soon as the patient has been properly prepared to withstand the surgical trauma. In peri-appendiceal and subphrenic abscesses, medical treatment alone is useless; surgical drainage must be carried out. Cases of generalized peritonitis secondary to intestinal perforations should be given aqueous penicillin (500,000 units intramuscularly every 4 hours) and streptomycin (0.5 gm. intramuscularly every 6 hours) for 12 to 14 days; treatment must be instituted before operation and continued for at least 12 days after surgery. Tetracycline (Achromycin), chlortetracycline (Aureomycin), oxytetracycline (Terramycin), chloramphenicol and other drugs have been used successfully in some instances. The drugs employed must be active not only against gram negative bacteria (*E. coli*) but also against gram-positive ones (fecal streptococci); some observers feel that it is more important to eradicate the latter. Streptococcal, pneumococcal or gonococcal peritonitis is best treated with penicillin in a dose of 250,000 units intramuscularly every 4 hours for 10 to 12 days. The management of tuberculous peritonitis is the same as for the pulmonary form of the disease (Chapter VII).

INTESTINAL INFECTIONS

Infections of the intestinal tract may be produced by bacteria, viruses, and amebae, are very common, and occur in all age groups. They are often short-lived and benign, but can be prolonged and complicated. They may be so mild that symptoms are inapparent, or so severe that death from fluid loss and shock ensues rapidly.

The organisms responsible for intestinal tract infections are transmitted by the fecal-oral route Contaminated food, flies, and feces are responsible for many sporadic episodes or epidemics of bacterial, viral, and amebic diarrhea. Man is the primary and intermediate host for some of the organisms. Non-immune individuals may contract disease from asymptomatic carriers or from persons with active or chronic infection. The enteric diseases are rife in crowded areas, particularly where sanitary practices are lacking or poorly applied. Animals or their products may also be a source of infection. Some mice and rats normally carry enteric pathogens, especially some species of *Salmonella*, in their bowel. The ingestion of food or water contaminated with the feces of these animals may result in disease. Chicken and duck eggs may also harbor organisms which produce intestinal infection in man. There have been several large epidemics of diarrhea following the use of commercially-prepared egg powder. *Salmonellae* are the commonest cause of "food poisoning" in man Flies act purely as mechanical vectors in transferring organisms from infected feces to food or water.

The intestinal tract reacts to injury of any type in a limited and relatively non-specific fashion Thus, regardless of the nature of the disease process, the general clinical pictures which develop are qualitatively quite similar, although variable in degree. The syndromes which characterize intestinal infection are produced by three mechanisms: (1) the constitutional reactions associated with invasion by infectious agents, (2) inflammation, irritation, and destruction of tis-

sue in the bowel, and (3) migration of organisms from the intestine to other organs by way of lymphatics or the blood stream, or by direct penetration into the peritoneal cavity. Ulceration and perforation of the bowel may lead to generalized peritonitis or the development of localized abscesses at various sites.

In the majority of intestinal infections, the organisms and the disease remain confined to the bowel; in some, however, they extend beyond the alimentary canal. For example, bacteria may invade the lymphoid tissue and migrate to lymph nodes where they produce reactions; they may penetrate the portal vein system leading to the development of pylephlebitis and multiple liver abscesses, or, they may reach the systemic blood supply and produce multiple metastatic areas of infection in distant organs.

The symptoms and signs related to the intestinal involvement are nausea, vomiting, localized or diffuse abdominal pain. This discomfort is usually cramping in character but may be sustained; its intensity may be mild to excruciating. Diarrhea is the commonest feature of intestinal infection and varies greatly in degree; in some cases, it is quite severe, with as many as 30 to 40 loose stools per day which contain blood, pus, and mucous shreds. In others, it is mild with only one or two soft stools per day. On the other hand, constipation may be the presenting feature, as in typhoid; it may be interspersed with bouts of diarrhea. Fever may be absent, remittent or intermittent, or sustained at high levels. Generalized malaise, anemia, and other manifestations consistent with infection are often present.

The white blood count in many of the intestinal infections is normal, unless some complication develops. In others, it may be elevated with an increase in neutrophiles from the onset of the disease. Blood cultures are frequently positive in some types (typhoid fever, staphylococcal enteritis) and practically always negative in others (bacillary or amebic dysentery, viral diarrhea). In bacterial infections of the

bowel, the stool often contains blood and numerous leu cytes. In amebic colitis, large numbers of erythrocytes, l no white cells, are usually present. The feces may contain abnormal cellular elements with viral diarrhea; blood or p or both, may, however, be present in some cases.

The presence of intestinal infection is usually suspected the basis of the general features described above and special ones discussed below. The cause of the disease be determined only by isolation of the responsible organi from the feces. With the exception of direct examination stool for amebae, stained or other preparations of fecal ma rial are of no value in etiologic diagnosis. One exception this is staphylococcal enteritis in which gram-stained sme of stool reveal the typical clusters of gram-positive cocci the only or the predominant organism.

The therapy of specific types of intestinal infection based entirely on the nature of the causative agent. Det of treatment for individual diseases are discussed below.

Bacillary Dysentery

Of all the bacterial diarrheas, 75 to 80 per cent are du dysentery bacilli. The carrier rate in many parts of world is high, in the United States it varies from 0.1 11 per cent in different parts of the country.

The organisms responsible for bacillary dysentery *Shigella shiga* and *Shigellae paradysenteriae;* of the la the Sonne and Flexner species are most common in United States. *Shigella shiga* is rare in this country, prominent in the tropics, the Orient, and some parts Europe. The organisms are gram-negative rods and are tinguished from *E. coli* by their failure to ferment lact (Sonne strains attack this sugar slowly), from the *Salmo lae* by their inability to produce gas in glucose, and from typhoid bacillus by their lack of motility.

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The lesions produced by dysentery bacilli are restricted

to the large bowel; in somewhat less than 50 per cent of cases, they extend to the terminal ileum but their intensity is less than in the colon. Diarrhea is often not present at the onset of bacillary dysentery. Generalized malaise and slight fever for 1 to 2 days, with or without loose stools, comprise the most frequent picture of the disease. In one outbreak, *the only manifestations* were nausea and vomiting. In severe infections, which occur especially in young children and elderly individuals, the diarrhea is profuse and the stools may resemble those of cholera. Fever is often of high degree. Shock may supervene early because of excessive loss of fluids and electrolytes and because of absorption of the endotoxins of the organisms. In most cases, however, diarrhea is mild and the disease terminates, without complication, in a few days. Some episodes of so-called "food-poisoning" which last for only one day may be to infection with dysentery bacilli. The incubation period of the disease is usually about 2 to 4 days, but it may be as long as a week.

Among the complications of bacillary dysentery are meningismus, pneumonia and agranulocytosis; these are observed most often in children. The disease may simulate acute appendicitis in the young age group. In adults, it may become chronic and persist with exacerbations and remissions for many years. This is most common in the Tropics. Individuals who have chronic bacillary dysentery often become symptom-free when they move to a colder climate; diarrhea often reappears, however, when they return to a warm area. Reiter's syndrome—urethritis, conjunctivitis, and arthritis—may develop 2 to 4 weeks after the onset of bacillary dysentery and is thought to be due to a reaction of hypersensitivity; a skin lesion closely resembling keratosis blenorrhagica appears in some cases. Perforation of the intestine is very rare, despite the presence of a considerable degree of ulceration. Pyelonephritis, empyema, glomerulonephritis, and otitis media may develop. Chronic bacillary dysentery may produce all of the anatomical and clinical

features of ulcerative colitis. Repeated attacks of Sonne and Flexner infection are relatively common because specific immunity does not last longer than 6 to 8 months.

With the exception of bacteriologic study, laboratory investigations are of little or no help in the diagnosis of bacillary dysentery. The white blood count is normal or elevated to between 10,000 and 15,000 per mm^3. Blood cultures are usually negative. In severe cases, microscopic examination of feces reveals leucocytes, erythrocytes, and mucous shreds. The most important diagnostic procedure is stool culture. Caution must be exercised, however, in assuming a causal relationship between the isolated organism and the disease, because of the possibility that a patient with some other type of intestinal disorder in which diarrhea is a feature (cancer, for example) may be a carrier. Serologic studies are not very helpful. Agglutinins against dysentery bacilli develop slowly. The titer may be very low after 2 to 3 weeks or longer; in some cases, agglutinins never appear.

The treatment of bacillary dysentery is relatively simple and effective. The administration of sulfadiazine or sulfisoxazole produces rapid relief of diarrhea and other symptoms. The dose of these drugs for adults is 4 gms. initially followed by 1 gm. every 4 hours orally; for children, it is 0.1 gm. per pound per day, one-half of the total dose being given as the initial one. Sulfaguanidine, sulfathalidine, and sulfasuxidine are also useful but are not as effective as the more rapidly absorbed sulfonamides. In some instances, the organisms may be resistant to these agents; in these, therapy with tetracycline or chloramphenicol, 0.25 gms. by mouth every 6 hours, is indicated. Treatment with any of the antibacterial drugs should be continued for 10 days. Although the antimicrobial agents are effective in eliminating the clinical manifestations, they do not always eradicate the carrier state which may persist for weeks or months.

Bacillary dysentery is easily preventable. In the face of

an outbreak, the administration of 0 5 gm. of sulfadiazine orally every 12 hours for 5 days to all contacts usually halts promptly the spread of infection; the active cases must be isolated. Chloramphenicol (0.25 gm. by mouth every 12 hours) is also an effective prophylactic. Vaccines for the prevention of bacillary dysentery are not sufficiently developed for practical application. Proper sanitation, control of flies, protection of food, water, and milk supplies, and not allowing carriers of dysentery bacilli to engage in the preparation or dispensing of food are fundamental to the prevention of this disease.

Salmonellosis

Many species of *Salmonella* produce infection in man. Although they may be separated very crudely on the basis of fermentation reactions, the only exact methods of identification involves antigen analysis using specially prepared antiserums. *Salmonellae* are motile gram-negative rods which do not ferment lactose and, with the exception of the typhoid bacillus, produce acid and gas from glucose. The commonest species which produces human infection is *S. typhi-murium;* next in order of frequency are *S. choleraesuis* (*S. suipestifer*), *S. newporti,* and *S. montevideo.*

Salmonellosis is most frequent in young children and old people; it is usually severe at these age extremes. Three clinical pictures may appear: (1) *Gastroenteritis* ("food poisoning"), (2) *Salmonella fever,* and (3) *Salmonella septicemia.*

The commonest form of salmonellosis is acute gastroenteritis. Because the organisms are frequently ingested in foods which have been contaminated by rodent feces or human carriers, or in duck or in chicken eggs, the syndrome has been called "food poisoning." The incubation period averages 18 to 36 hours, although it may be as short as 8 hours or as long as 3 days. As a rule, the first symptoms are

nausea and vomiting. Abdominal cramps are frequent and may be very mild or excruciatingly severe. Fever may be absent, of low degree, or high and "spiking"; chills occur occasionally. There may be only 1 or 2 loose stools in mild cases; in severe ones, the diarrhea is often profuse and bloody. In very young children and elderly people the disease may simulate cholera. On the average, symptoms are present for about 3 to 4 days, although they may last only one day or persist for weeks. Chronicity develops in some instances and is featured by remissions and exacerbations of marked diarrhea, fever, and abdominal pain. The white blood count is usually normal, although it may be elevated. Blood cultures are rarely positive. The stool contains blood and leucocytes when the diarrhea is severe. Septic complications are uncommon, except in young children. The carrier state appears in some instances without relation to the severity of the acute episode.

Salmonella fever is produced most often by the paratyphoid bacilli—*S. paratyphi*, *S. schottmulleri*, and *S. hirschfeldi*. The clinical picture resembles typhoid fever qualitatively but is usually milder. Fever is of variable degree and duration; it may be high, intermittent, remittent, or sustained, and last for from 1 to 3 weeks. Although diarrhea is present in many cases, patients may be constipated or have no gastrointestinal symptoms. Bradycardia and splenomegaly are common. Rose spots are infrequent. Bacteremia occurs often. Bronchitis and bronchopneumonia may develop, the causative organisms are present in the sputum. *Salmonellae* may not be demonstrable in the feces until many days or up to several weeks after the onset of infection. They may appear in the urine later in the course of the disease. Leucopenia with relative lymphocytosis is the rule.

Salmonella septicemia is most often due to *S. choleraesuis* and is the most serious of the infections produced by this group of organisms. Intestinal symptoms are usually absent in most adults; in children, on the other hand, acute gas-

troenteritis appears early in the course of the disease. The main features of the syndrome result from hematogenous spread of the bacteria to different organs or from their presence in the blood. A high, often "spiking", fever with frequent chills is usual. Bradycardia relative to the height of the temperature is frequently observed; tachycardia is present in some cases. The white blood count is elevated or depressed; leucopenia is most common.

Metastatic infections may occur during Salmonella septicemia, and lead to the development of meningitis, osteomyelitis, or pneumonia. Other less common complications are endocarditis, purulent arthritis, pyelonephritis, and abscesses in the subdural space, spleen, muscles, and other soft tissues. In elderly adults there is more than a chance association between aneurysms of the aorta (usually arteriosclerotic) and susceptibility to Salmonella septicemia. The prognosis in this form of the disease is poor.

The death rate in salmonellosis is about 20 per cent. Most fatalities occur in the septicemic form of the disease and are due to infection with *S. choleraesuis.* Four species account for three-fourths of the deaths—*S. choleraesuis, S. typhimurium, S. oranienberg,* and *S. newporti.* A fatal outcome is most frequent in patients over 50 years of age and in children less than one year old; in the latter, acute gastroenteritis is common. The development of meningitis, pneumonia, peritonitis, endocarditis, or other metastatic infections decreases the chance for recovery.

The clinical diagnosis of salmonellosis is difficult. Although the possibility of this type of infection must be considered in every case of diarrhea regardless of its mildness or duration, other organisms produce acute gastroenteritis so frequently that it is impossible to suspect the etiology on the basis of the signs and symptoms alone In the absence of intestinal manifestations, the nature of the disease is often not apparent, and it is labelled an "obscure fever." The specific diagnosis can be established only by isolation of the

organisms from the stool and demonstration of a significant increase in the serum agglutinin titer. In Salmonella fever or septicemia, the causative agents may not be present in the feces at all, or appear only days to weeks after the onset of the disease. In these cases, blood culture is the only method *of making a diagnosis. Serologic studies are necessary when* the organisms cannot be isolated; serums obtained 12 to 14 days apart should be titrated for specific agglutinins. The initial titer, unless high, is of no diagnostic value since it may represent previous exposure or immunization.

Most cases of acute gastroenteritis due to *Salmonella* are so mild and of such short duration that they require no specific therapy. In those which are more severe or prolonged, the drug of choice is chloramphenicol; a dose of 0.25 gm. orally every 6 hours suffices in most instances to cure the symptoms. It must be stressed that this is not always immediately successful. For Salmonella fever or septicemia the same antimicrobial agent is used; quantities as large as 4 to 6 gms per day may need to be given for at least 2 to 3 weeks, relapses requiring retreatment may occur. The problem of the carrier state has not been solved by chemotherapy; this may develop as often after very mild, short-lived episodes as after more serious or prolonged disease. Its incidence has not been remarkably decreased by treatment of the acute stage of infection with potent antimicrobial agents. Most people who become Salmonella carriers harbor the organisms in their intestine or biliary passage about 30 to 40 days after onset of illness; this may be prolonged to 10 to 12 weeks. In uncommon instances, the carrier state is permanent. Since the administration of antibiotic agents such as chloramphenicol *is often not successful in* solving this problem, it is good practice to withhold treatment if symptoms are not present because the danger of drug reactions outweighs any possible benefit. Although chemotherapy has been given to patients in whose stools the organisms are still detectable after 3 or 4 months, in most

instances it is probably best not to treat such individuals but to restrict them from preparing or serving food.

The prevention of Salmonella infection cannot be effected, as in dysentery, by the use of antimicrobial agents. Proper sanitation, control of carriers, elimination of flies, and boiling or cooking of potentially contaminated food or water are the essentials of effective prophylaxis. Immunization against *S. paratyphi* and *S. schottmulleri* (paratyphoid A and B) has been carried out for many years. The degree of its effectiveness is still a matter for critical evaluation. However, vaccination against these organisms as well as the typhoid bacillus is advisable for persons planning to travel to or reside in areas where these diseases are common.

Typhoid Fever

The incubation period of typhoid fever is 1 to 2 weeks. The onset of the disease is variable. It may be insidious with low-grade fever and mild symptoms of the "grippe." Occasionally it starts with marked elevation of temperature, chills, severe headache, and constipation or with symptoms suggestive of nervous system involvement such as headache, delirium, meningeal irritation, and even acute mania. Fever, chills, cough, and signs of bronchopneumonia, or severe abdominal pain and vomiting may be the first manifestations. Very rarely, the first sign is an abscess in one of the organs.

The course of untreated typhoid fever during the first week is characterized by a steady, step-wise increase in fever up to 104° to 105°F. where, with minor fluctuations, it tends to remain steady. Less frequently, the fever may be low grade or a "spiking" temperature may be present. Chills are uncommon. There is relative bradycardia. Slight tenderness and distension of the abdomen are often present. Constipation is more frequent than diarrhea. Delirium is usually absent. At about the end of the first week, splenomegaly (70

per cent of cases) and rose spots appear. The skin lesions are irregular, pink macules (generally less than a dozen in number) *which blanch on pressure, appear in crops on the* anterior walls of the chest and abdomen, yield typhoid bacilli on culture, and occur in about 90 per cent of white patients.

During the second week all of the manifestations tend to be aggravated. The fever remains at a high sustained level. Tachycardia often replaces the slow pulse rate. The characteristic mental torpor, a peculiar, sluggish, low grade dementia, from which the disease derives its name, appears at this time. Abdominal symptoms become more marked, distension and tenderness of the abdomen increase in severity, and diarrhea is more frequent. Death may occur during this period, especially in patients with severe nervous system *manifestations, or those who suffer hemorrhage or perforation* of the intestine. In mild cases, the disease may terminate at the end of the second week.

The third week in moderately severe typhoid fever is characterized by decreased fever, tachycardia, pulmonary and cardiac involvement, and intestinal complications. Bronchopneumonia, lobar pneumonia, pleural effusion, or pulmonary infarction may develop. Dicrotic pulse, hypotension, changes in the heart sounds (they become soft and distant), varying degrees of heat block, systolic murmurs, electrocardiographic changes of myocarditis, endocarditis or pericarditis may appear. Intestinal perforation or hemorrhage is a constant threat; the former occurs in 3 per cent and the latter in 7 per cent of cases. While both are most common in the third week of infection, they may appear as early as the second or as late as the sixth week; they are most frequent in cases in which abdominal pain and distension are marked. Convalescence begins by the end of the third week in most instances. In some, however, the disease persists, and weakness, marked weight loss, constant muttering delirium, subsultus tendinum, carphologia, and

circulatory failure are the outstanding factors. Some patients die at this point; others continue to have symptoms for one or two more weeks and finally recover or die.

A large number and variety of other complications may occur during the course of typhoid fever. Furuncles, purpura, herpes simplex, and gangrene are the manifestations which develop in the skin. Complete and irreversible alopecia, involving particularly the scalp, may appear. Parotid swelling accompanied by uveitis is observed occasionally; this is Heerford's syndrome. Conjunctivitis, keratitis, iritis, panophthalmitis, acute glossitis, spontaneous rupture of the spleen or rectus muscles, pulmonary infarcts, hemoptysis, hepatomegaly with jaundice, multiple liver abscesses, suppurative cholangitis, acute and chronic cholecystitis, pyelonephritis, osteomyelitis, spondylitis, and perispondylitis involving the lumbar and sacral regions (Gibney spine), suppurative arthritis, meningitis, mono- or polyneuritis, cerebral vein thrombosis, and localized abscesses in various organs (thyroid, cervical lymph nodes, breast, spleen, muscles of the legs and buttocks, and appendix) have also been described.

Relapses develop in 10 per cent of cases of typhoid fever. They may be of 3 types. (1) The *ordinary relapse* occurs from 1 to 6 weeks after defervescence, and may be repeated as many as 3 to 5 times, prolonging the duration of the disease for many months. The clinical picture may be more severe than the initial episode and death may result. (2) The *intercurrent relapse* appears at a time when fever is still present; all of the manifestations become exaggerated. (3) Secondary elevations in temperature without increase in the clinical activity of the infection characterize the *spurious relapse.*

Unless the cardinal manifestations of typhoid fever are present, the diagnosis is very difficult to make clinically. Many cases present as "obscure" fevers. Although rose spots, splenomegaly, fever, chills, and constipation suggest the

disease, the only methods of confirming its presence are bacteriologic and serologic. The typhoid bacillus can be isolated from the blood in 90 per cent of cases in the first week of infection; in the second week, the incidence of bacteremia is reduced to between 50 to 75 per cent, in the third week to 25 to 50 per cent, and in the fourth week to about 10 per cent. Stool cultures are positive in 5 to 10 per cent of patients in the first, 25 to 50 per cent in the second, 75 to 90 per cent in the third, and 50 to 75 per cent in the fourth week of illness. The organisms are present in the urine of 25 per cent of cases in the third and 10 per cent in the fourth week. Thus, early in the disease, blood culture is of greatest diagnostic help, while cultures of the stool or urine are most important later. Serologic tests establish the diagnosis when organisms cannot be isolated, and confirm it when they have been recovered. The Widal test (agglutination) is positive 10 to 14 days after onset. A rise in agglutinin titer when acute and convalescent phase serums are compared is most significant. Single determinations, unless high, greater than 1:160, are of little value since they may merely reflect prior exposure to the typhoid bacillus or immunization. The level of H and O agglutinins aid in differentiating antibody associated with infection from that which follows injection of vaccine. With active disease, the O antibody titer is much higher than the H. The opposite is true after immunization. Information relative to previous exposure or immunization must be obtained in all cases before the significance of an elevated titer is interpreted.

The treatment of typhoid fever has changed considerably since potent antimicrobial agents have become available. However, certain principles of management still apply. Thus, it is very important to insure an adequate food intake ("bland" diet) and normal water and electrolyte balance, *and to maintain a careful watch for the* appearance of treatable complications. Chloramphenicol is the drug of choice for the specific therapy of the disease. Several sched-

ules of treatment have been employed. The writer prefers the following one: two grams of the antibiotic are given initially and are followed by 1 gm. orally every 4 hours until defervescence has occurred; therapy is then continued with 1 gm. every 6 to 8 hours for an additional 3 weeks. White blood counts and differentials must be carried out at least every other day. If leucopenia of a significant degree appears, especially if the neutrophiles are markedly decreased in number, the drug should be withdrawn immediately; otherwise, irreversible aplasia of the bone marrow may supervene. Hemorrhage and perforation of the bowel occur in treated cases. The main reason for prolonged therapy is to reduce the risk of relapse. This still occurs, however, in an appreciable number of instances, and is thought to be due to suppression of immunity by early, intensive treatment. Several alternate regimens have been suggested to overcome this difficulty. One procedure involves immunization with typhoid vaccine during the administration of chloramphenicol. In another, "rest" periods of 3 to 4 days are interspersed with antibiotic therapy for 5 days over a period of 3 to 4 weeks. The effectiveness of these programs remains to be proved. Cortisone has been used, in addition to chloramphenicol, for the first 3 to 4 days of therapy by some clinicians for the purpose of rapidly abolishing severe clinical manifestations. Several objections to this procedure may be raised. (1) Fever, chills, and severe symptoms vanish quickly when sufficiently large doses of antimicrobial agent alone are employed. (2) Since intestinal ulceration is a prominent feature, perforation and hemorrhage may be hastened by the use of cortisone. Regardless of the dose of chloramphenicol used and the length of time over which it is applied, the carrier state develops in an appreciable number of patients. Very little is accomplished by re-treatment in most instances. In some individuals who become permanent carriers, cholecystectomy may be helpful if the bacteria are present only in the wall of the gall bladder. In

others, however, this operation is unsuccessful because the organisms are present in the intrahepatic biliary system where they produce chronic cholangitis.

The early recognition and treatment of complications of typhoid fever command serious attention. Relapses must be managed in the same way as the initial attack. Intestinal hemorrhage and perforation must be kept in mind constantly. An abrupt change in the clinical course with the appearance of tachycardia, hypotension, abdominal pain (not always striking if the patient is delirious), distension and loss of peristaltic sounds, and rapidly developing anemia suggest the development of one of these catastrophes. As soon as the patient can be prepared for surgery by the use of fluids, blood, vasopressor agents, etc., laparotomy should be carried out. The severity of the illness does not contraindicate the operation for without closure of the bleeding vessel or perforation death results.

There is no chemoprophylaxis for typhoid fever. Prevention of the disease involves the principles of sanitation applicable in other enteric infections Immunization has been very widely applied. Although many observers consider this procedure entirely effective, there is some doubt of its efficacy in the minds of others. This is so because improvements in sanitary practice were made at about the same time typhoid immunization was introduced, it has thus been difficult to determine which factor has been responsible for the reduction in incidence of typhoid fever in parts of the world where both measures have been employed. Despite this uncertainty, it is best to administer typhoid vaccine to all individuals who reside in or travel to areas where the disease occurs frequently. Protection is not produced in 100 per cent of subjects. Primary immunization should be followed by yearly booster doses in persons who are constantly exposed. In the face of disasters, war, earthquake, storms, etc., when water supply and sewage disposal are interrupted, it is best to protect the entire population. Boiling

of water, chemical disinfection of excreta, and proper cooking of potentially contaminated milk and food reduce considerably the spread of enteric disease.

Acute Staphylococcal Enteritis and Staphylococcal Food Poisoning: Pseudomembranous Colitis

Acute staphylococcal infection of the intestine is rarely a primary disease. It is usually secondary to the use of antimicrobial agents (oral preparations, especially) which produces changes in the intestinal bacterial flora. This entity must be distinguished from staphylococcal food poisoning, which is not a bowel infection, but a syndrome caused by a toxin elaborated by some strains of staphylococci. The organisms produce the enterotoxin most often and in largest quantities when growing in foods which contain carbohydrate. Ingestion of this food results in an acute gastroenteritis with fever, nausea, vomiting, abdominal pain, severe diarrhea, and often bloody stools. If the intoxication is sufficiently severe, shock and even death may occur. The incubation period is 4 to 12 hours. The causative staphylococci cannot be recovered from the stool and the lesions in the bowel wall are not due to invasion by them. There is no specific therapy, except replacement of lost water and electrolytes.

Acute staphylococcal enteritis is characterized by invasion of the intestine by the organisms which produce tissue destruction and ulcer formation. The staphylococci responsible for the disease are usually present in the bowel and become predominant when the microbial flora is altered by the administration of various antibiotic agents. The responsible strains are insensitive to the drug which provokes the disease. Fever, chills, abdominal pain, and profuse diarrhea containing blood and numerous leucocytes are the outstanding manifestations. Shock may supervene. The staphy-

lococci may invade the blood stream in some instances and produce metastatic infection in many areas, including the brain, endocardium, lungs, and joints. Any of the available antibiotic agents may be responsible for this syndrome but the "broad spectrum" drugs are especially prone to produce it. It may appear after either oral or parenteral administration. The possibility of acute staphylococcal enteritis must be considered in patients who develop diarrhea during or shortly after treatment with an antimicrobial agent. It can be confused, however, with the diarrheas which result from the irritative effects of antibiotics.

An entity which requires differentiation from acute staphylococcal enteritis is pseudomembranous colitis. This may also follow the use of chemotherapeutic agents, particularly the "broad spectrum" drugs. Acute necrosis of the mucous membrane of the colon, severe constitutional reaction and the same intestinal manifestations that are observed in staphylococcal infection of the bowel are present. The syndrome may develop in patients who are not receiving antibiotics, especially if they have been subjected to intestinal surgery. There is some question whether the administration of antimicrobial agents actually predisposes to the development of this disorder.

The diagnosis of staphylococcal food poisoning can be established only on epidemiological grounds and by demonstrating that the bacteria *recovered from the suspected food* produce an enterotoxin. The presence of acute staphylococcal enteritis is proved by isolation of hemolytic, coagulase-positive *Staph. aureus* from the feces, where they are predominant or the only organism present. Gram-stained smears of the diarrheal stool often reveal myriads of gram-positive cocci in typical grape-like clusters. It must be emphasized that demonstration of a few colonies of *Staph. aureus* in fecal cultures may have no significance because this organism is frequently present in the bowel microflora

of normal individuals. The diagnosis of pseudomembranous colitis is difficult to make. Stool cultures often reveal a marked predominance of *Proteus* and *Ps. pyocyanea* in many cases.

There is no therapy for staphylococcal food poisoning except repair of disturbed water and electrolyte balances and the management of shock, if it occurs. The most important step in the treatment of acute staphylococcal enteritis is withdrawal of the drug which provoked it. In some cases this results in prompt cessation of diarrhea as a result of re-establishment of the normal bacterial bowel flora which overgrows the staphylococci. However, this alone is not sufficient in many instances. In these, the administration of bacitracin (0.5 gm. every 6 hours) or neomycin (0.5 gm. every 6 hours) *by mouth* should be started after stools have been obtained for bacteriologic study. A combination of chloramphenicol and erythromycin (0 5 gm. of each orally every 6 hours) may be used if neither of these was being given at the time the disease appeared. The organisms isolated from the feces must be examined for sensitivity to antimicrobial agents in all instances; if the drugs being administered are ineffective, the one to which the staphylococci are most susceptible must be given. Parenteral therapy is indicated when bacteremia or metastatic foci of infection are present. Neomycin and bacitracin are not absorbed from the intestinal tract and must be injected intramuscularly if a systemic effect is desired. Once therapy is initiated it should be continued for 2 to 3 weeks.

The treatment of pseudomembranous colitis starts with the elimination of the provoking antimicrobial agent and correction of water and electrolyte disturbances. In many instances, this is sufficient to stop the diarrhea. If the intestinal manifestations persist, 0.5 to 1 gm. of neomycin orally every 6 hours per day may be of help, therapy should be continued for 10 to 14 days.

E. Coli Diarrhea

Pathogenic strains of *E. coli* have been incriminated as the cause of diarrhea in young children. These organisms can be differentiated from other strains by fermentation reactions and antigen analysis; some of the types have been labelled 0-55, 0-55 B, 0-111, 0-111-B4, and 0-127 B8. The *enteritis which they produce is relatively mild and is* characterized by diarrhea and abdominal distension with little or no fever. The stools are said to have a characteristic pungent, musty, objectionable odor which is different from that noted in other types of diarrhea.

The possibility that pathogenic *E. coli* are responsible should be considered in every young child with diarrhea. Mere isolation of coliform organisms from the stool is not diagnostic, since the invasive strains cannot be distinguished from those of the normal intestinal flora on the basis of cellular and colonial appearance; special fermentation tests *and antigenic pattern determinations are necessary. These* are not carried out in routine laboratories. Therefore, in cases in which no other enteric pathogens can be demonstrated and the clinical findings are suggestive, treatment for *E. coli* diarrhea should be initiated. The therapy of choice is neomycin, 50 mg. per Kg. per day in divided doses orally, for 7 to 10 days. There is no risk of toxicity to the eighth cranial nerve and the kidney because the drug is not absorbed from the intestinal tract.

Tuberculous Enteritis

Although the stomach has been found to be involved in about 2 per cent of cases of tuberculosis at necropsy, the lower portion *of the ileum and the cecum are the areas of* the gastrointestinal tract most often infected The affected

of normal individuals. The diagnosis of pseudomembranous colitis is difficult to make. Stool cultures often reveal a marked predominance of *Proteus* and *Ps. pyocyanea* in many cases.

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the disease such as the lungs. The diet should be bland. The ingestion of "rough" foods may provoke episodes of severe diarrhea and abdominal pain.

Amebic Dysentery

Amebic dysentery is not limited to the tropics. Between 5 and 10 per cent of the population of the United States have been found to harbor amebic cysts in the intestine; acute outbreaks of the disease have been observed in this country. Cyst carriers who remain in the temperate zone usually have no symptoms; within a short time of migration to a warm climate, however, diarrhea may develop. The patient with amebic dysentery in the tropics may lose all symptoms and become an asymptomatic carrier when he moves to a colder area.

The clinical picture of intestinal amebiasis is not characteristic. The most common syndrome is not even suggestive of colitis and consists of fatigue, headache, pronounced "nervousness," and a rise in temperature in the afternoon. In some cases, postprandial epigastric distress, gaseous eructation, or nausea and vomiting are present. In the most severe disease, the diarrhea is constant, the fever high, and the white blood count elevated with a relative increase in neutrophiles. Diarrhea resembling dysentery occurs in only about 5 per cent of patients About 25 per cent have intermittent loose stools interspersed with periods of normal bowel evacuation or constipation; fever is moderate and present intermittently, and the white blood count is usually normal The stools usually contain blood, but no pus, unless secondary infection has taken place.

Amebiasis may consist of a single severe episode followed by an asymptomatic state during which the only indication of disease is the presence of cysts in the stool. It may be featured by repeated relapse and remission or become subacute and then persist in chronic form for a long period

portion of bowel is the site of superficial ulcerations which may extend rapidly and become widespread or remain localized and become chronic; perforation is uncommon. In the cecum there is often a proliferative granulomatous lesion, which is protracted and produces marked thickening of the wall with fibrinous peritonitis and narrowing of the intestinal lumen. This may form a mass which is difficult to differentiate from a tumor. Most cases of tuberculosis of the intestinal tract are secondary to pulmonary infection and swallowing of organisms. Some are primary infections and are due to ingestion of contaminated milk (often the bovine strain); others follow tuberculous peritonitis or hematogenous dissemination of the organisms from other sites.

The first manifestations of tuberculous enteritis do not suggest bowel disease and consist merely of moderate weight loss, vague indigestion, and anorexia. A little later, short episodes of diarrhea interspersed with periods of normal bowel function or constipation occur. After weeks or months, true diarrhea with 10 to 20 loose, watery, stools which rarely contain blood and cramping lower abdominal pain appear. Other signs of tuberculosis (marked weight loss, fever, anemia, etc.) become progressively more noticeable.

The possibility of tuberculous enteritis is suspected in individuals with tuberculosis of the lungs or other organs who develop diarrhea. Physical examination of the abdomen may be entirely unrevealing or may elicit tenderness and spasm in the right lower quadrant suggestive of appendicitis. The appendix is sometimes the site of extension of infection from the cecum. Roentgenographic study of the bowel is suggestive but not diagnostic, filling defects, spasticity, hypermotility of the lower ileum, cecum, and ascending colon may be observed.

The treatment of tuberculous enteritis is the same as for other forms of tuberculosis (Chapter VII); as a matter of fact, therapy of the intestinal tract infection is often incidental to the management of other more common foci of

demonstrate the trophozoites. The accuracy of this type of diagnosis is directly related to the experience of the observer searching for the amebae.

Very helpful and often the only method of making the clinical diagnosis of amebic colitis is proctoscopic examination. Careful study by this method in early cases of the disease reveals yellow elevated nodules of pinhead size, or very small ulcers with hemorrhagic margins which look like superficial snail tracks. In the full-blown dysenteric cases, larger ulcers with undermined rugged edges varying in size from 2 to 3 mm. to 2 to 3 cm. in diameter, with very little reaction surrounding them, and with bases covered by gray mucoid material (made up mostly of amebae) are observed; these lesions are produced by the cytolytic activity of a substance which the organisms secrete. In patients who have chronic amebiasis or who are asymptomatic cyst carriers, the lesions usually appear as small depressions (pits) which may be so minute in size that they are easily overlooked. All of these stages are seen in some individuals. When amebae cannot be demonstrated in stools, they can sometimes be found by obtaining material for study directly from the floor of the ulcers. Organisms are usually absent when the disease resembles ulcerative colitis.

The diagnosis of amebic hepatitis should be suspected in patients with clinical evidence of liver disease in whose stools trophozoites are demonstrable When a liver abscess develops, drainage by needle will yield necrotic material in which amebae can be demonstrated

A complement-fixation test is available for the diagnosis of amebiasis, but it is difficult to perform. The reaction is usually negative in amebic colitis but positive when hepatitis is present It may be positive with severe amebic dysentery or liver abscess but is not invariably so. On the whole, this test is of relatively little help in diagnosis

The use of emetine in the treatment of amebic colitis has been almost completely discarded because, although the

of time. In patients with chronic amebic colitis, especially children, the skin has a dusky, faded sun-tan appearance, even in the winter.

A number of complications appear during the course of intestinal amebiasis. Hepatomegaly, with or without symptoms, occurs in about 10 to 15 per cent of adults. Some of these have amebic hepatitis with multiple areas of necrosis in the liver, high fever, tender hepatomegaly, and leucocytosis; jaundice and abnormal liver function tests are infrequent. The hepatic lesions coalesce to form one or two large abscesses. In addition to the signs and symptoms described above, diaphragmatic involvement with pain in the right shoulder and roentgenographic evidence of elevation and fixation of the right diaphragm are often present. An amebic abscess is located most often in the posterior aspect of the right lobe of the liver and, if it points towards the body wall, may be visible or palpable in the right upper quadrant of the abdomen. It may perforate the diaphragm with resultant pleural, pulmonary, or pericardial involvement or may invade the abdominal cavity and neighboring hollow viscera. Amebae may escape into the circulation and produce abscesses in various organs including the brain. Arthralgia which usually does not respond well to salicylates may also complicate amebic colitis. The patient with chronic recurrent attacks of intestinal amebiasis may develop a clinical and anatomical picture indistinguishable from ulcerative colitis.

The possibility of amebiasis of the intestine should be suspected in all individuals who have diarrhea, particularly if it tends to be recurrent, or becomes chronic, and pathogenic bacteria cannot be isolated from the stool. The only method by which the specific diagnosis can be established is by demonstrating the organisms in the bowel or feces. The discovery of cysts is of no significance, since they may represent only a carrier state. Stools should be examined on a warm-stage microscope as soon as evacuated in order to

demonstrate the trophozoites. The accuracy of this type of diagnosis is directly related to the experience of the observer searching for the amebae.

Very helpful and often the only method of making the clinical diagnosis of amebic colitis is proctoscopic examination. Careful study by this method in early cases of the disease reveals yellow elevated nodules of pinhead size, or very small ulcers with hemorrhagic margins which look like superficial snail tracks. In the full-blown dysenteric cases, larger ulcers with undermined rugged edges varying in size from 2 to 3 mm. to 2 to 3 cm. in diameter, with very little reaction surrounding them, and with bases covered by gray mucoid material (made up mostly of amebae) are observed; these lesions are produced by the cytolytic activity of a substance which the organisms secrete. In patients who have chronic amebiasis or who are asymptomatic cyst carriers, the lesions usually appear as small depressions (pits) which may be so minute in size that they are easily overlooked. All of these stages are seen in some individuals. When amebae cannot be demonstrated in stools, they can sometimes be found by obtaining material for study directly from the floor of the ulcers. Organisms are usually absent when the disease resembles ulcerative colitis.

The diagnosis of amebic hepatitis should be suspected in patients with clinical evidence of liver disease in whose stools trophozoites are demonstrable. When a liver abscess develops, drainage by needle will yield necrotic material in which amebae can be demonstrated.

A complement-fixation test is available for the diagnosis of amebiasis, but it is difficult to perform. The reaction is usually negative in amebic colitis but positive when hepatitis is present. It may be positive with severe amebic dysentery or liver abscess but is not invariably so. On the whole, this test is of relatively little help in diagnosis.

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The use of emetine in the treatment of amebic colitis has been almost completely discarded because, although the

drug is effective, it is cardiotoxic in some individuals. Less dangerous agents have been substituted for it. Treatment with combinations of drugs appears to be most successful. For mildly ill, ambulatory patients, Diodoquin (0.65 gm. 3 times a day for 20 days) plus chloraquine (1 gm. for 2 days followed by 0.5 gm. at bed time for 18 days) has been suggested. If the symptoms do not clear or if systemic manifestations, dysentery and hepatitis are present, one of the following regimens is employed: (1) Chloraquine (same doses as above) plus oxytetracycline (Terramycin) (0.5 gm. orally every 6 hours) for 20 days. (2) Milibis (bismuth glycolylarsanilate) (0.5 gm. 3 times a day) together with Terramycin or Aureomycin (0.25 to 0.5 gm. orally every 6 hours). For amebic hepatitis or early small liver abscess, Carbarsone (0.25 gm. 3 times a day for 10 days) or combined therapy with Chloraquine and one of the antibiotics are indicated. In cases with large, accessible liver abscess, needle aspiration is the first procedure; if this is unsuccessful, open drainage must be carried out. Treatment with emetine may become necessary in some instances. This drug should not be given until an electrocardiogram has revealed a normal myocardium. The dose is 60 mg. subcutaneously once a day for 3 days; Chloraquine and an antibiotic should be administered at the same time, in the manner described above.

Viral Diarrhea

Viruses are probably common causes of diarrhea. While this type of disease has been observed and studied most extensively in children, there is little doubt that it also occurs in adults. Viral diarrhea often appears in epidemic form. A number of severe outbreaks have been described in nurseries; the source of infection has been shown in some instances to be a recently delivered mother with mild gastroenteritis just prior to or at the time of parturition.

Several types of viral diarrhea have been described. One variety occurs mainly in 8 to 9 day old children. It has an incubation period of about 7 days, suggesting that it is probably contracted at the time of birth, when the opportunity for contamination with maternal feces is greatest. Intestinal manifestations are uncommon early in the disease; the outstanding findings are *drowsiness and refusal of food.* Diarrhea appears after 1 to 2 days As the infection gains headway, the dysentery becomes severe; *the stools are fluid,* yellow, and usually do not contain mucus, blood, or pus. Dehydration and shock follow unless water and electrolyte disturbances are repaired An agent which produces diarrhea when fed to calves has been demonstrated in the intestinal contents of patients with this disease.

Another type of viral diarrhea, Dodds-Buddingh disease, is almost completely restricted to infants but occurs rarely in adults. The outstanding features are intestinal manifestations and vesicular stomatitis and glossitis. The average incubation period is 2 to 3 days. Most of the patients are 3 days old, indicating infection at the time of birth. The stools are green and contain a considerable quantity of mucus and, in some cases, streaks of bright red blood. Vesicles are present on the anterior border, tip, and undersurface of the tongue; occasionally, they may also be found on the gums and the inner surface of the lips. These lesions rupture in 1 to 2 days and leave superficial bleeding excoriations. Dehydration and shock may occur but are not common. The disease may, however, be very severe and death may occur in premature infants.

A new group of viral agents has recently been isolated from the stools of normal children and from some with diarrhea, these are the "enterorespiratory" viruses. They can be cultivated in tissue culture. There are at least 13 different antigenic types. Since some strains of the agent have not been associated with specific disease states and have been

demonstrated in healthy individuals, they are now referred to as enteric cytopathogenic human "orphan" (ECHO) viruses.

The diagnosis of viral diarrhea is usually made on the basis of the exclusion of bacterial or amebic infection. It is very important to emphasize the fact that many outbreaks in newborn infants are due to *Salmonellae* or dysentery bacilli. For this reason, and because these infections can be eliminated by antibiotic agents, it is imperative that stool cultures be carried out in every case.

There is no specific treatment for viral diarrhea. The outcome of the disease is influenced to a very great degree by the speed and accuracy with which the metabolic disturbances—dehydration and electrolyte imbalances—are corrected. This aspect of treatment cannot be overemphasized. *The earlier and the more effectively such therapy* is carried out, the lower the fatality rate. Adequate facilities for chemical studies must be available. Overhydration is to be avoided because of the risk of fatal pulmonary or cerebral edema.

CHAPTER X

INFECTIONS OF THE LIVER, BILE DUCTS, GALL BLADDER AND PANCREAS

INFECTIONS OF THE LIVER

A variety of infectious agents may produce disorders of the liver. Some infections, particularly those due to bacteria, are most often secondary to invasion from other organs, particularly the intestinal tract or gall bladder. Others appear to be primary, without evidence of disease elsewhere in the body. The term hepatitis, as commonly used, connotes a specific type of liver disease, but actually includes all forms of inflammatory reactions, whether produced by living agents or toxic substances.

Like most other organs, the varieties of response of the liver to injury, regardless of the nature of the responsible agent, are relatively limited. The clinical picture which develops with hepatic infections is made up of 7 main components. (1) *Manifestations of infection:* Fever of varying degree is present in most cases of hepatitis and may be accompanied by chills in some instances. Elevation of temperature is common, however, in many noninfectious types of liver disease, such as toxic reactions and even tumors. Malaise, generalized aching, and weakness are frequent. Manifestations of upper respiratory tract infection, especially sore throat, are often present for a variable period prior to the appearance of hepatic involvement. (2) *Gastro-*

intestinal manifestations: Symptoms and signs of dysfunction of the gastrointestinal tract appear in most infections of the liver. Anorexia is a frequent complaint; it may be very severe. Nausea is often present and is accompanied, in most instances, by vomiting. Enlargement of the liver produces pain in the right upper quadrant of the abdomen. Constipation or diarrhea may be prominent; the former is more common. (3) *Hepatomegaly and jaundice:* Although not detectable very early in the course of some cases of hepatitis, hepatomegaly practically always becomes apparent as the disease progresses. The liver is tender and the edge is usually smooth, sharp or rounded; percussion over the lower right lateral chest wall often elicits moderate discomfort or sharp pain. Splenomegaly is detectable in many cases. Jaundice is present in most hepatic infections, but its absence does not rule out this type of disorder. It frequently is not apparent in the early stages of some kinds of hepatitis or may not be observed during the entire course of the illness, even when it is prolonged. (4) *Physical signs of hepatic dysfunction:* In the more severe types of hepatic infection, physical evidence of functional derangement often appears. It has been suggested that this results from inability of the liver to metabolize properly estrogen, antidiuretic hormone, and aldosterone. As a result, telangiectases (elevated, small red spots from which fine, clearly outlined blood vessels arborize peripherally) appear on the skin. Although they may be present in any location, they are most commonly found about the clavicles, and on the wrists, dorsa of the hands, and face. The same mechanism may be involved in the development of "liver palms" (reddening of the thenar and hypothenar eminences of the hand) and facial acne which are commonly observed. Increase in aldosterone has recently been proposed as the responsible factor. Salt and water retention occur and produce gain in weight and perceptible edema in some cases. Diuresis often precedes and heralds a favorable turn in the course of hepatitis: as a rule,

jaundice begins to decrease in intensity 1 to 2 days after the urinary output increases. (5) *Laboratory evidence of general hepatocellular dysfunction:* Evidence of cellular dysfunction appears at some time in most forms of liver infection; it may not be present early when clinical manifestations are minor. Decreased bromsulfalein excretion is *practically always detected. Positive cephalin flocculation* and thymol turbidity reactions are common; they may be due to disturbances in the relationship of various serum proteins, and must always be evaluated in this light before their significance in an instance of suspected liver disease is accepted. In the most severe cases of hepatitis, prothrombin content is decreased, the levels of serum albumin, cholesterol esters and blood urea nitrogen are low, and hippuric acid synthesis is inhibited. Fecal and urine urobilinogen are usually increased if antibiotics have not been given. The quantity of indirect reacting bilirubin in the serum is elevated. Biliuria is a constant finding when jaundice is present. (6) *Laboratory evidence of "obstructive jaundice": The early phase of most hepatic infections is accompanied* by swelling of the liver cells with blocking of the biliary canaliculi, which produces chemical changes consistent with obstruction of bile flow. Thus, in the early stages of many cases of viral hepatitis, there is an increase in immediately reacting (1 minute) bilirubin and in serum alkaline phosphatase levels. The stools may be acholic and urobilinogen reduced or absent from the stool and urine. (7) *Other clinical and laboratory manifestations:* In addition to the skin changes described above, rashes of various types may appear in some infections of the liver. Morbilliform, urticarial, vesicular, and petechial eruptions have been described. The white blood count is normal or depressed and the lymphocytes increased in number in most types of hepatitis Bacterial or leptospiral infections are usually accompanied, however, by leucocytosis.

The diagnosis of infection of the liver is often difficult

because many of the signs, symptoms, and laboratory abnormalities are also present in noninfectious hepatic disorders or can be detected in the absence of liver disease. Although the combination of fever and jaundice is highly suggestive of hepatic infection, it may also be observed in toxic hepatitis, alcoholic cirrhosis, liver tumors, and hemolytic anemias in crisis. On the other hand, icterus may be absent even when very extensive infection of the liver is present, as in miliary tuberculosis, for example. Jaundice itself is not indicative of hepatic disease since it is observed in hemolytic anemias and after the ingestion of such drugs as atabrine. Hepatomegaly or splenomegaly are not diagnostic since they occur in a wide variety of disorders. Telangiectases and "liver palms" are found frequently during pregnancy. The chemical and flocculation tests of liver function are not specific. While biliuria and alterations in urobilinogen excretion are highly suggestive of liver disease, they do not necessarily indicate infection. Although impairment of bromsulfalein excretion and abnormal cephalin flocculation and thymol turbidity reactions are consistent with hepatocellular damage, they are not diagnostic of an infectious process. Despite the non-specificity of all of these features, their presence should, nevertheless, arouse suspicion of the possibility of liver infection.

It is frequently difficult or impossible to make a diagnosis of hepatitis in the early stages because many of the suggestive findings are absent. In such instances, the epidemiological background and, most important, the changes which occur during the course of the disease often reveal its etiology. The possibility of exposure to toxic agents which produce liver damage must be excluded in any case in which fever and abnormal liver function tests are present. In some cases, the nature of the hepatic disorder remains obscure despite thorough clinical and laboratory study; it may even be impossible to differentiate between obstructive

and hepatocellular disease. In such instances, it is occasionally helpful to perform a liver biopsy. It must be stressed, however, that even this procedure may fail to yield diagnostic information if, by chance, the needle enters an unaffected area of the liver.

The purpose of therapy of hepatic infections is two-fold; (a) eradication of invading organisms, if possible, and (b) *protection of the liver against further damage.* Disease produced by bacteria, leptospirae, and amebae can be treated with drugs; the type of agent administered depends on the nature of the causative organism There is no specific treatment for the viral hepatitides. Measures employed to protect the liver include proper diet and rest. The dietary management of acute hepatitis has changed considerably over the last few years. A diet high in protein and carbohydrate, but low in fat, no longer appears to be essential. The feeding regimen employed at present consists of an increased quantity of carbohydrate and normal amounts of fat and protein. An excessive intake of protein should be avoided when liver dysfunction is severe because ammonia poisoning may develop. Although methionine, choline, and crude liver extract are frequently administered, their value has been questioned by some observers The need for "strict" bed rest in hepatitis has recently come under close scrutiny. Studies have indicated that, except in severe cases, no harm is produced by allowing patients to be out of bed for variable periods; as a rule, the individual sets his own limit for mobilization. Enforced bed rest seems not only unnecessary but probably unwise in children with viral hepatitis because the disease is usually very mild.

Little can be done to prevent bacterial infections of the liver except to eradicate the sources from which they arise. The leptospiral diseases may be decreased in incidence by eliminating contact with the animals or their products from which the organisms are transmitted to man. *Protection can*

be produced against one form of viral hepatitis (IH) by the administration of gamma globulin prepared from normal plasma. The details of prophylaxis in specific situations are described in detail below.

Viral Hepatitis

Viral hepatitis is produced by two distinct agents. One is responsible for infectious hepatitis (IH) and the other for homologous serum jaundice or serum hepatitis (SH).

Infectious Hepatitis (IH)

Infectious hepatitis is a common disorder. The virus to which it is due is present in the stool and blood of patients at least 3 days before symptoms appear and for a minimum of 8 days after jaundice develops. The agent has not been demonstrable in the feces of recovered cases longer than one month after the onset of infection. Fecal—oral transmission is most common. Contaminated water, food, and milk have been incriminated in some instances. Although it has been suggested that dissemination of the virus may take place by way of the respiratory tract, opinion on this point is not settled. Contaminated needles and syringes may also be responsible for spread of the disease; this is the only method of transmission in serum hepatitis (SH). IH infection has been produced in human volunteers by the feeding and injection of blood or the ingestion of dried feces of active cases

Infectious hepatitis involves primarily children, although it may occur at any age. Individuals between 10 and 14 years old are the most susceptible. The misconception of prevalence in adults stems from experience in the armed forces in which patients up to 30 years of age have been most frequently affected. Susceptibility decreases after the age of 30. One episode usually produces lasting immunity; second attacks appear in about 3 to 5 per cent of cases.

The incubation period of infectious hepatitis is approximately 20 to 40 days. The disease is qualitatively the same in children and adults. It is milder, in general, in the young age group and the height of the fever, intensity of the gastrointestinal manifestations, duration of jaundice, and risk of complications are less. The infection in youngsters typically begins with headache, fever, abdominal pain, and vomiting. The temperature may rise to 102°F. and usually persists at this level for 4 to 5 days, disappearing as jaundice develops; all the symptoms ameliorate at this time. Icterus is present for about 10 to 12 days. Complications are very uncommon and death is rare.

A form of IH infection which is most common in children but may be observed also in adults is characterized by absence of visible jaundice; this is "non-icteric" or anicteric hepatitis. Fever and gastrointestinal manifestations or elevation of temperature alone are the most common symptoms. The liver is usually enlarged Hepatomegaly and fever persist for 1 to 2 weeks. If relapse occurs, icterus may appear. Laboratory studies reveal evidence of hepatocellular dysfunction.

In most adults and in many children, infectious hepatitis is divided into 2 stages· (a) the pre-icteric phase, and (b) the phase in which jaundice is the outstanding manifestation. About 85 per cent of patients have symptoms of illness for from 2 to 3 to 7 to 10 days before icterus becomes apparent. The most frequent (100 per cent) complaint during this period is severe anorexia. Smokers develop a great distaste for tobacco. Generalized aching, headache, nausea, vomiting, abdominal pain, and fever are common. Sore throat is prominent in some cases. The abdominal pain is often located in the epigastrium or right upper quadrant. Diarrhea or constipation may be present. The temperature may rise to 104° to 105°F. and be intermittent; chills occur occasionally.

A variety of skin eruptions may appear during the pre-

icteric phase; morbilliform, scarlatiniform, urticarial, or vesicular rashes have been observed. A severe meningoencephalitis may rarely be the only manifestation. Physical examination is usually not helpful in this stage of the disease. Tenderness to percussion and enlargement of the liver are detectable in some instances. Visible jaundice is absent. Laboratory studies not infrequently reveal decreased bromsulfalein excretion and abnormal flocculation reactions. Leucopenia is the rule. The detection of liver dysfunction is usually the only basis for suspecting the presence of the anicteric stage of infectious hepatitis.

The appearance of jaundice is, as a rule, associated with a striking amelioration of signs and symptoms; this is not always the case, however. In most patients, the temperature rapidly returns to normal. Appetite is commonly regained and *abdominal pain, nausea, vomiting,* and *generalized* aching disappear. The jaundice varies considerably in intensity and duration. It may be slight and present for only 1 to 2 days or severe and persist for 4 to 5 months. The average duration is 20 to 30 days, the peak usually being reached in about 10 days. Reappearance of fever and other manifestations is indicative of relapse or extension of the process in the liver.

Physical examination during the icteric phase reveals a varying degree of enlargement of the liver which is smooth and tender. Splenomegaly is present in only a small number of cases. Bradycardia is frequently detectable. Yellow discoloration of the sclerae and skin is the rule. Telangiectases ("spiders") and "liver palms" are observed in the more severely ill patients. While loss of weight is usual because

Early in the icteric stage laboratory studies often reveal changes consistent with biliary obstruction. Thus, acholic stools, biliuria, absence of urobilinogen in the feces and

urine, increased serum alkaline phosphatase, and elevated levels of direct-reacting (1 minute) bilirubin in the blood are common. Within a short time, however, evidence of hepatocellular damage appears, as indicated by return of bile in the stools, high levels of urobilinogen in the urine and feces, normal alkaline phosphatase, a rise in indirect-reacting serum bilirubin, and positive cephalin flocculation and thymol turbidity tests Jaundice and biliuria are present. Bromsulfalein excretion and flocculation reactions become abnormal 3 to 5 days after the onset of infection. A decrease of serum albumin and an increase in globulin are common, especially in severe cases. The urine often contains albumin, particularly during the febrile phase. The white blood count is normal or decreased with a relative increase in lymphocytes. In most cases, "abnormal" lymphocytes indistinguishable from those detected in infectious mononucleosis are present in varying numbers in the peripheral blood; the heterophile agglutination reaction is negative, however.

The clinical course of infectious hepatitis is variable. Most patients recover completely, the liver healing without scarring or other residual damage Marked asthenia is very common in the majority of cases and may persist for 3 to 6 months. Some individuals complain of recurrent anorexia, ease of fatiguability, vague abdominal discomfort, and weight loss. When these manifestations are severe, careful investigation should be carried out to exclude the chronic or subacute stage of hepatitis In most instances, however, no abnormalities are detected; the syndrome is very suggestive of neurocirculatory asthenia.

Relapse has been described in from 2 to 18 per cent of cases of infectious hepatitis. There may be no clinical manifestations, but laboratory studies reveal evidence of recurrence of liver dysfunction. The relapse may be similar to the primary episode or may be more severe.

When activity is present in infectious hepatitis for 2

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months or longer, the disease is classified as subacute. From this stage, the infection may take one of three courses: (a) full recovery, (b) progressive hepatic failure, or (c) gradual development of cholangiolitic biliary cirrhosis. The frequency with which infectious hepatitis becomes chronic is not known; the risk of its development is greatest in patients in whom remissions and exacerbations of liver damage and dysfunction have characterized the acute and subacute stages of the disease. Pregnancy increases the severity of infection in the acute phase and predisposes to chronicity and cirrhosis; exacerbation of the hepatic progress may follow parturition. It has been suggested by one observer that 6 per cent of patients with infectious hepatitis develop cirrhosis of the liver. This incidence appears to be too high; the exact degree of risk of this complication is not known. The factors which are thought to favor the development of hepatic fibrosis are (1) heavy physical exertion, (2) poor diet, (3) ingestion of alcohol, (4) intercurrent infections, and (5) accidental or surgical trauma to tissues. The overall fatality rate is low, however, usually less than 4 per 1000.

The diagnosis of infectious hepatitis is based on epidemiological information regarding contact with the virus (not often available), the presence of general manifestations of infection, and clinical and laboratory evidence of liver involvement. The course of the disease is often sufficiently characteristic to suggest the diagnosis. Cholangitis, leptospirosis, serum hepatitis, infectious mononucleosis, toxic hepatitis due to carbon tetrachloride and other chemical agents may be confused with infectious hepatitis. Carefully obtained histories, evidence of other diseases, and the course of illness sometimes suggest the specific etiology. In some instances, liver biopsy may be helpful; because of the limited range of reaction of liver cells to injury, however, this procedure is not always of value.

The diet for patients with infectious hepatitis (IH) should contain a large amount of carbohydrate, about 1 to

1.5 gms. of protein per Kg. of body weight per day, and a quantity of fat sufficient to make meals palatable. Some physicians continue this diet for 2 to 3 months after recovery. Strict bed rest is not necessary except in the most severely ill cases. Most patients voluntarily restrict their physical activity to a degree compatible with their comfort and safety. Unusual exertion and ingestion of alcohol are contraindicated during the acute phase of the disease and for a period of 6 to 12 months after recovery. The need for choline, methionine, and crude liver extract cannot be clearly proved, although these agents are frequently administered. Vitamin supplements are helpful in the individual who has anorexia, but do not appear to be necessary when food intake is adequate.

Determination of exercise tolerance is a good test for recovery of liver function. When all clinical and chemical evidence of hepatic disturbance has disappeared, running or walking a patient up and down a flight of stairs 2 to 3 times may quickly produce abnormalities in liver function tests and so reveal that full recovery has not yet taken place.

Cortisone has been given in the acute phase of very severe cases of infectious hepatitis. Although symptoms are suppressed, proof that corticosteroids alter the course of the infection is not available. Therapy with these agents must be reserved for patients with overwhelming disease; it is possible that, in such instances, it may be life-saving. The writer is opposed to the administration of these drugs early *in viral infections because they may provoke dissemination* of the infectious agent.

Antibiotics, particularly the tetracycline compounds, have been used in the treatment of infectious hepatitis. They have no demonstrable action on the virus. In severe cases, they may produce a beneficial effect by reducing the total number of bacteria in the intestinal flora. The rationale of this is as follows. Organisms in the bowel metabolize ingested protein to yield ammonia and other products which

circulate in the blood. In normal individuals, these substances are detoxified by the liver. When, however, hepatic function is impaired, toxic levels of ammonia accumulate. By reducing the intestinal flora with antibiotics, less ammonia is formed and presented to the diseased liver.

Infectious hepatitis (IH) is preventable. Autoclaving of needles and syringes, restricting the use of a single needle to a single patient, and prohibiting patients who have had the infection from acting as blood donors for at least 2 years are important in decreasing the incidence of the disease. Stool precautions of the type employed in the enteric infections (exposure of all feces to 95 per cent phenol solution for one-half hour, and aseptic precautions on the part of personnel in contact with cases) are helpful in reducing the risk of spread on a hospital ward. Proper chlorination of water is also important in certain situations. For individuals or groups of persons who have been exposed to a case of infectious hepatitis, prophylaxis with gamma globulin obtained from pools of normal plasma is very effective. The dose is 0.02 ml. per pound of body weight; the maximal quantity given to adults is 10 ml. The greatest degree of protection *is afforded* when the *material is injected intramuscularly* within 3 to 4 days after exposure, it may be beneficial up to 10 days after contact.

Serum Hepatitis (SH)

Homologous serum jaundice, or serum hepatitis, is probably also a viral disease although the agent which produces it has not yet been identified. The infection is transmissible only by parenteral routes; the causative organism is present in the blood but not in the feces. Young adults are the most highly susceptible, unlike infectious hepatitis (IH), older individuals develop the disease quite frequently. There are several points of differentiation of IH from SH (Table 1).

TABLE 1

DIFFERENTIATION OF INFECTIOUS AND SERUM HEPATITIS

	I.H.	S.H.
Incubation Period	20-40 days	40-160 days
Virus in Feces	Yes	No
Virus in Blood	Yes	Yes
Experimental Infection	Parenteral or Oral	Parenteral Only
Clinical Course	Generally Mild	Generally Severe

The clinical features of serum hepatitis are indistinguishable in most instances from those of infectious hepatitis. In many cases of homologous serum jaundice, however, laboratory tests indicative of hepatic dysfunction are strongly positive before marked clinical changes appear; the opposite is true of IH infection. In general, the course of SH is more severe than that of IH, and the fatality rate and risk of development of subacute and chronic liver disease are higher.

Without a known exposure to potentially contaminated needles or syringes, or blood or plasma transfusion within 40 to 160 days prior to the onset of disease, it may be impossible to differentiate serum hepatitis from infectious hepatitis. In cases of SH with short incubation periods, a history of parenteral exposure may not be of diagnostic help because as long as 40 days may elapse between contact with IH virus and the beginning of that illness. Furthermore, as pointed out above, infectious hepatitis may also be produced by the parenteral route. Lack of cross immunity between the two diseases may be of some help in diagnosis. This can be demonstrated by means of a skin test with egg-

grown IH virus. The reaction is positive in patients recovered from infectious hepatitis but not in those who have had serum hepatitis. This test is still used only experimentally.

The treatment of serum hepatitis is the same as for infectious hepatitis. There is no immunologic method of prophylaxis for SH; the use of gamma globulin is of doubtful value. However, certain measures are effective in reducing spread of the disease. No patient who has had jaundice should act as a blood donor for at least 2 years; some investigators are of the opinion that such individuals should not give blood for transfusion for the rest of their lives. No plasma pool should be the product of more than 2 donors. Plasma is safest when obtained from a single person. The incidence of hepatitis following transfusion of plasma obtained from large pools of blood is about 20 per cent. All needles and syringes should be autoclaved. If this is not possible, boiling in water for 20 minutes is adequate. Immersion in alcohol does not destroy the infectious agent. It has been suggested that ultraviolet irradiation of plasma may be helpful in preventing serum hepatitis; this has not proved to be 100 per cent effective, however. Allowing plasma pools to stand at room temperature for 2 to 3 months is another method claimed to destroy the SH "virus"; this observation needs confirmation. The use of albumin and fibrinogen injections may be followed by homologous serum jaundice; it has never been observed after the injection of gamma globulin.

Suppurative Cholangitis

Suppurative cholangitis, with or without liver abscesses, usually follows bile stasis due to scar, stone, or tumor in individuals with previous infection of the biliary tract, the organisms spreading by extension along the bile ducts into the liver. Direct extension may occur from infected gall bladder, subphrenic abscess, or other suppurative lesion in

the vicinity of the liver. When the gall bladder is the source of infection, cholelithiasis is invariably present.

The organisms most often responsible for suppurative cholangitis are *E. coli* and fecal streptococci. The clinical picture is characterized by fever which may be "spiking", chills, colicky abdominal pain, jaundice, hepatomegaly, liver tenderness, and occasionally splenomegaly. A variant of this syndrome is the so-called Charcot triad. This follows obstruction of the common bile duct by stones. Its main manifestations result from the accompanying cholangitis and are chills, fever, and jaundice; *pain is absent*. There is usually high grade leucocytosis with a marked increase in neutrophiles in acute cholangitis. The urine contains bile and an excess of urobilinogen due to the destructive hepatic lesion. Other laboratory evidence of biliary obstruction and hepatocellular damage is present. Blood cultures are occasionally positive.

The differentiation of suppurative cholangitis from infectious hepatitis is sometimes difficult. This is emphasized by the fact that, despite exhaustive studies, patients with viral infection of the liver are occasionally subjected to exploratory laparotomy under the erroneous impression of cholelithiasis and cholangitis. Laboratory tests of hepatic function are often of little help. The features of acute cholangitis which may be of help in distinguishing it from viral hepatitis are as follows: (1) The generalized manifestations and the other features of the pre-icteric phase of infectious hepatitis are usually absent. (2) There is usually a history suggestive of chronic cholecystitis and cholelithiasis (x-ray study of the gall bladder is unrevealing in the acute case). (3) Duodenal drainage yields material which contains leucocytes and crystals of calcium bilirubinate or cholesterol, or both. (4) The clinical picture is often featured by a "spiking" temperature and chills after jaundice has appeared, in contrast to infectious hepatitis in which a fall in temperature is common as icterus develops and becomes

more pronounced. (5) The white blood count is elevated with a relative increase in neutrophiles. (6) Liver biopsy reveals abscesses in the periportal areas in some cases and the bile ducts contain polymorphonuclear leucocytes; (7) Properly selected antibiotic treatment often produces a beneficial effect; caution must be exercised, however, in making an etiologic diagnosis on the basis of a therapeutic response.

The treatment of suppurative cholangitis involves both medical and surgical management. Chemotherapy must be directed against both gram positive and negative organisms. Several therapeutic regimens are effective. The administration of benzyl penicillin G (1,000,000 units every 4 to 6 hours) plus 0.25 to 0.5 gm. of streptomycin every 6 hours intramuscularly is beneficial in many cases. Chlortetracycline (Aureomycin) or tetracycline (Achromycin) (0.5 gm. *orally every 6 hours) is also worth a trial.* Another combination of drugs which may be of value is chloramphenicol (0.5 gm. every 6 hours) and streptomycin (same dose) given by intramuscular injection. Therapy should be continued for 12 to 14 days. Spontaneous improvement occurs not infrequently, particularly when obstruction is partially relieved by a shift in position of a stone in the common bile duct. Surgical treatment—drainage of the gall bladder and common bile duct, with or without cholecystectomy—should not be delayed for more than one week unless the infection is definitely subsiding

Liver Abscesses

Multiple abscesses of the liver usually are secondary to foci of infection outside of this organ and are much more common in the right than the left lobe. The bacteria which cause hepatic suppuration reach the liver by several routes: (1) via the portal vein by means of septic emboli, or following a pylephlebitis resulting from appendicitis, disease

of the intestinal wall as in typhoid fever, or superimposed bacterial invasion of bowel ulcers, (2) along the bile ducts (cholangitis), (3) through the hepatic artery during bacteremia (infrequent), and (4) by direct introduction into the liver through wounds.

The organisms present in most cases of liver abscesses are *E. coli*, *Staph. aureus*, streptococci, the Friedlander bacillus (*K. pneumoniae*), dysentery bacilli, *Entamoeba histolytica*, and rarely *Clostridium welchii* and other anaerobic bacteria. When the disease is secondary to a wound, a large variety of microorganisms may be involved.

The outstanding manifestations in patients with multiple liver abscesses are those of severe infection. "Spiking" fever, frequently accompanied by chills, drenching sweats, and extreme weakness are very common. The liver is tender, painful, and enlarged, the right lobe being most intensely involved is often pushed upward producing elevation and immobility of the right diaphragm. Cough and pain in the right shoulder and chest result from diaphragmatic irritation. Right lumbar backache and tenderness to percussion over the right costovertebral angle are usually present. Nausea and vomiting may be pronounced. Jaundice is usually not noted; the highest reported incidence is 50 per cent but is usually less than this. Icterus appears most often when there is an associated cholangitis. Ascites develops when the disease is secondary to pylephlebitis. Hepatic abscesses may rupture through the diaphragm and produce empyema, or into the peritoneal cavity and lead to the development of peritonitis, or into the subphrenic space and result in the formation of a subdiaphragmatic abscess.

The white blood count in patients with liver abscesses is usually elevated to levels of 15,000 to 30,000 or higher with a marked increase in neutrophiles. Laboratory evidence of hepatic dysfunction is often absent despite the fact that the lesions are numerous and widespread. However, impaired

bromsulfalein excretion as well as positive cephalin flocculation and thymol turbidity reactions may be present when a diffuse inflammatory reaction develops.

The diagnosis of liver abscesses is difficult. The disease is suspected most often in patients with appendicitis, acute or chronic cholecystitis, or intestinal infections who develop the clinical picture described above. Infectious (IH) or homologous serum (SH) hepatitis may present a similar syndrome, but an important differential point is the elevated white blood count with suppurative disease of the liver. Acute cholangitis is often difficult to differentiate, particularly since it is occasionally complicated by the development of multiple hepatic abscesses.

The prognosis in untreated patients with multiple liver abscesses is poor, the fatality rate being over 90 per cent. Treatment consists of the use of large quantities of antibiotics; the drugs of choice and their doses have been described above in the discussion of the therapy of suppurative cholangitis. When the liver disease is secondary to staphylococcal bacteremia, penicillin (benzyl G) in quantities as large as 10,000,000 units per day, or chloramphenicol plus erythromycin (2 gms. of each per day) are the regimens of choice. Therapy should be continued for at least 2 to 3 weeks. Surgical drainage of lesions which serve as foci for the hepatic infection—ruptured appendix, acutely inflamed gall bladder, for example—must be carried out.

Leptospirosis (Weil's Disease)

Liver disease may be produced by several species of *Leptospira*, the commonest ones being *L. icterohemorrhagiae*, *L. canicola*, and *L. pomona*. *L grippotyphosa* and *L. autumnalis* cause infection less commonly.

Swine, dogs, cats, rats, and mice harbor the organisms. Although they may become severely ill and die when infected, they often recover and continue to shed the lepto-

spirae in their urine as a result of a chronic nephritis. The milk of cows may also transmit leptospirae. The portals of entry in man are the respiratory and gastrointestinal tracts, and the skin. Certain occupations are associated with a high predilection to the disease as a result of frequent exposure to rats or their urine. These include sewer workers, ditch diggers, coal miners, farmers, poultry cleaners, fish handlers, and other individuals who work in areas where there are a large number of rats. Weil's disease has been described in persons not exposed to infection by virtue of their occupation. Swimming in contaminated water or contact with the infected urine of an apparently healthy family dog account for some such non-occupational cases.

The incubation period of leptospirosis is 8 to 12 days. The disease occurs most often in the summer, since the organisms are killed by exposure to cold It is a diffuse infection in which multiple manifestations generally occur. The degree of severity is variable. In some cases, only fever and a rash are seen. In others, a severe hepatitis with or without an accompanying acute nephritis is the outstanding finding. Diagnosis may be difficult because the infection may masquerade as a simple "grippe" syndrome or as moderately severe "aseptic" meningitis

Leptospirosis is uncommon in children Individuals over 30 years of age are most likely to develop it in the severest form. Young adults and adolescents experience the milder disease

In severe, full-blown leptospirosis, the onset is abrupt with one or more shaking chills followed by fever which may rise to as high as 104°F. Pain and tenderness in the lumbosacral spine and in the calves of the legs are so intense that slight movement or handling of these areas may produce excruciating discomfort. Cough and sore throat may develop early. Nausea, vomiting and diarrhea may be present. Severe headache and photophobia are very common. Suffusion of the conjunctivae is striking. Iridocyclitis with

ocular pain and circumcorneal inflammation may also be observed. Optic neuritis occurs rarely. Petechial eruptions appear in severe cases; scarlatiniform and morbilliform rashes are uncommon.

Involvement of the liver occurs in about 60-70 per cent of case of Weil's disease due to *L. icterohemorrhagiae*, *L. canicola*, and *L. grippotyphosa*. It is less frequent when *L. pomona* is the responsible agent. Hepatitis usually develops after fever has been present for 4 to 7 days. The liver is enlarged and tender. Splenomegaly is not frequent. Jaundice appears and is accompanied by biliuria, although the stools are not acholic. The icterus usually increases for the first 2 to 4 days and then subsides after 7 to 10 days.

About 50 per cent of the patients who have leptospiral hepatitis develop an acute nephritis which appears at about the end of the first week. Oliguria and anuria as well as hematuria, albuminuria, pyuria, and cylindruria characterize this feature of the illness.

The white blood count is generally elevated to levels between 12,000 and 25,000 cells per mm^3. In patients with hepatitis there is an elevation in serum bilirubin. Cephalin flocculation and thymol turbidity reactions are frequently abnormal.

Signs of meningeal irritation may appear at any time in the first week. The spinal fluid contains 10 to 250 cells, most of which are neutrophiles early in the disease, but these are replaced almost completely by lymphocytes later. The protein is increased, but the sugar content is normal. Xanthochromia of the cerebrospinal fluid is common in jaundiced patients. Unlike other diseases in which icterus is present, the spinal fluid in leptospirosis is yellow even when the icteric index is relatively low. This is an important point in differential diagnosis.

In the majority of cases of leptospirosis which survive, recovery is gradual. Marked asthenia is common for some time after termination of most of the signs and symptoms

which disappear in most instances after about 2 weeks. When hepatitis and nephritis are present, recovery requires a longer time. Relapses occur in approximately 20 per cent of the infections; severe head and muscle pains and fever are the usual manifestations of the recurrence. Second attacks of hepatitis and nephritis are rare, however. The prognosis is poorest when severe hepatic and renal involvement, deep jaundice, azotemia, oliguria, or circulatory impairment are present. The fatality rate in severe leptospirosis is 5 to 10 per cent.

The possibility of leptospirosis should be suspected in individuals with fever and leucocytosis who are exposed by their work to the risk of infection When chills, fever, leg and back pain, conjunctivitis, petechial eruptions, leucocytosis, hepatitis, and nephritis are present, the diagnosis is almost certain. Difficulty arises in cases in which only a "grippe" syndrome or "aseptic" meningitis appears.

A presumptive diagnosis of leptospirosis can be made in the first few days by biopsy of the gastrocnemius muscle. Microscopic examination reveals focal areas of necrosis, cellular reaction composed primarily of sarcolemnal nuclei, rare inflammatory cells, and absence of vascular changes.

Leptospirae can be recovered from the blood or urine of patients. Direct examination of blood in the first 5 days of the disease may reveal the organisms; this procedure must be carried out only by experienced personnel because strands of fibrin and other extraneous material may be confusing Leptospirae are present in the urine in about 25 per cent of cases during the second and third week of illness. They can be cultured from blood and urine by inoculation into a medium consisting of an agar-meat infusion base diluted with 0 85 per cent sodium chloride solution or water and enriched with 2 to 5 per cent serum or defibrinated blood. The organisms will also multiply in 12 per cent rabbit serum diluted with distilled water or on the chorioallantoic membrane of embryonated chicken eggs.

One of the most certain methods of demonstrating leptospirae in patients is inoculation of blood obtained in the first week of the disease into mice, guinea pigs, or hamsters. The animals sicken 3 to 15 days after infection.

In addition to isolation and identification of the organism, a very good method of establishing the diagnosis of Weil's disease is to demonstrate a rise in the agglutinin titer in the serum. Significant levels of antibody appear in the third and fourth week of disease. A rise in titer to 1:10,000 or 1:1,000,000 is not uncommon when acute and convalescent phase serums are compared.

Although animal experiments suggest that penicillin and Aureomycin (chlortetracycline) cure leptospirosis, experience with naturally occurring disease in man have not confirmed this impression. Controlled studies have revealed little difference in the duration, course, and outcome of the infection in treated and untreated cases. Despite this, however, it is probably best to give chemotherapy to severely ill cases of Weil's disease. The drugs which may be used and their doses are as follows: (1) Crystalline benzyl penicillin G—5,000,000 to 20,000,000 units in divided doses intramuscularly per day; (2) Aureomycin—1 gm. orally every 6 hours. Therapy should be continued for 12 to 14 days.

Infections of the Gall Bladder

Acute Cholecystitis

Acute infection of the gall bladder is associated with cholelithiasis in about 90 per cent of cases. As evidenced by absence of bacteria and pus in the bile, about 50 per cent of all episodes of acute cholecystitis cannot be related to bacterial invasion. Organisms may be present in the gall bladder and produce no difficulty unless there is biliary stasis usually due to obstruction of the cystic duct by a stone. Bacteria may also reach the gall bladder by way of the blood or lym-

phatic vessels. The resulting inflammatory reaction varies in severity from mild edema to gangrene, and often extends to the surrounding tissues.

The outstanding manifestations of acute cholecystitis are abdominal pain and the general symptoms and signs of infection. Fever may be high and "spiking" in character. Chills are not rare. The pain may start gradually and increase in severity or may be explosive in onset and colicky in nature. In either case, it usually becomes marked and persistent, being present mainly in the right upper quadrant of the abdomen. In about 10 per cent of cases, mostly elderly individuals, there may be very little discomfort. Nausea and vomiting are common.

Physical examination reveals spasm or rigidity and tenderness in the right upper quadrant, this is often slight in elderly individuals. In about 50 per cent of patients there is a palpable tender mass in this area which represents the enlarged gall bladder and adherent omentum. Jaundice is present in about 25 per cent of cases. There is usually a leucocytosis of 15,000 to 20,000 or more white blood cells per mm^3 with a relative increase in neutrophiles.

In many instances the disease subsides in 1 to 4 days. In about 40 per cent of cases, however, it is progressive and produces such complications as suppurative cholangitis, multiple liver abscesses, pyelophlebitis, acute pancreatitis, and empyema, gangrene or perforation of the gall bladder with peritonitis.

In cases in which cholelithiasis is known to be present, the diagnosis is usually not difficult when fever, chills, severe right upper quadrant pain, spasm, tenderness and a palpable mass are accompanied by leucocytosis. The distribution of pain may cause confusion, however, with such diseases as coronary artery occlusion, acute pleuritis, pneumonia, pulmonary infarction, acute pancreatitis, severe hepatitis, tumors of the liver, perforation of a viscus, or mes-

enteric vascular occlusion. In doubtful instances, studies to rule out these conditions must be carried out. In elderly individuals the possibility of acute cholecystitis should be suspected when unexplained fever and leucocytosis are present because there may be little or no pain. Minimal abnormalities in the right upper quadrant of the abdomen may be detected.

The treatment of acute cholecystitis is both medical and surgical. The organisms which are involved include both gram positive and negative forms. Aqueous penicillin (500,000 units intramuscularly every 4 hours) plus 0.5 gm. of streptomycin intramuscularly every 6 hours are often very effective. Aureomycin, tetracycline, or chloramphenicol (0.5 gm. orally every 6 hours) may also be useful. Occasional cases are due to the Friedlander bacillus; therapy in these should consist of 1 gm. of chloramphenicol plus 0.5 gm. of streptomycin intramuscularly every 6 hours. Penicillin is the agent of choice in the rare case produced by the *Pneumococcus*. If the manifestations subside rapidly, drainage or removal of the gall bladder may be delayed until the patient is fully recovered. If, however, the disease appears to be progressing, surgical treatment should be carried out promptly. It is unwise to temporize too long because of the risk of gangrene, perforation, and diffuse peritonitis.

Chronic Cholecystitis

Chronic infection of the gall bladder may follow acute inflammation or appear without preceding acute cholecystitis. The organisms which cause this type of infection are those which are normally present in the intestine—*E. coli, A. aerogenes, Proteus, K. pneumoniae,* and fecal streptococci. In patients who have had typhoid fever or other types of salmonellosis, the bacteria responsible for these diseases may produce chronic infection of the gall bladder wall and bile; this is responsible for the permanent carrier state in some instances.

Most cases (80 per cent) of chronic cholecystitis are associated with cholelithiasis. There are usually no striking *manifestations of infection* unless an acute inflammatory reaction supervenes. The outstanding symptom is intolerance to fatty foods the ingestion of which produces belching *and discomfort in the right upper quadrant of the abdomen* with referral, in many instances, to the right scapula. Repeated attacks of moderate to severe biliary colic may occur. *In patients in whom fat intolerance and abdominal discomfort* are not associated with the presence of gall stones, but in which a "non-filling" gall bladder is demonstrated, the manifestations are often functional and persist despite cholecystectomy.

Other than an attempt to control symptoms by reducing fat intake, there is no medical therapy for chronic cholecystitis and cholelithiasis. The treatment of choice is removal of the gall bladder.

Infections of the Pancreas

Bacterial and viral infections of the pancreas are very uncommon and are rarely, if ever, primary. Involvement of this organ may occur during the course of mumps and is usually present with other manifestations such as parotitis and meningitis; it may rarely be the only organ affected by the disease. The anatomical changes in mumps pancreatitis are edema and petechial hemorrhages, the picture is entirely different from that observed in hemorrhagic pancreatitis.

The outstanding symptoms of mumps pancreatitis are upper abdominal pain, nausea, and vomiting. Fever is always present and epigastric tenderness is common. The white blood count is frequently elevated.

Increase in serum amylase is often present but is not *diagnostic because it is practically always detected* when severe parotid involvement occurs. In very mild salivary gland infection, however, elevation of serum amylase as-

sumes greater importance. A rise in the level of serum lipase is of much greater diagnostic significance. There are no complications of mumps pancreatitis; chronic fibrosis or diabetes mellitus do not occur.

Multiple abscesses of the pancreas may arise in the course of acute hemorrhagic pancreatitis. They are often caused by *Staph. aureus,* although gram-negative bacteria may also be responsible. Large doses of penicillin, streptomycin, or other antimicrobial agents may be of some help, but definitive treatment is surgical drainage, without which survival is usually impossible.

CHAPTER XI

INFECTIONS OF THE URINARY TRACT

Infections of the Urinary Tract—General Features

Infection of the urinary tract is one of the commonest and most important of the disorders which afflict man. Recent studies have emphasized its wide-spread nature and the frequency with which it remains undetected because of the absence of symptoms, particularly when pyelonephritis is present. Patients with unsuspected urinary tract infections frequently experience silent progression of the process until irreversible renal and vascular changes occur; after many years, they end their lives in the explosion of a cerebral hemorrhage, the invalidism of heart failure, or the misery of uremia. The importance of a high index of suspicion of this disease on the part of physicians, the use of all the diagnostic procedures available for confirmation of its presence, and the institution of all possible medical and surgical therapeutic measures cannot be overemphasized. The exercise of careful clinical judgment may prevent the development or delay the pernicious course of this type of infection.

Although it occurs in completely normal persons, a number of factors, the commonest of which is some type of obstructive lesion, may predispose to the appearance of urinary tract infection. These are: (1) *Congenital Defects:* Congenital defects which produce any degree of block to urine flow and which are situated in any area from the urethral meatus to the renal pelvis often set the stage for bacterial invasion.

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bacteria from the intestinal tract to the kidney via the lymphatic vessels may occur. (6) *Metabolic Disorders:* The increased susceptibility of patients with diabetes mellitus to infection is well-known; the urinary tract is involved in a great many cases. Metabolic diseases with stone formation and obstruction—osteitis fibrosa cystica, cystinuria, and gout, for example—predispose to bacterial invasion of the bladder and kidneys.

There are 3 routes by which bacteria reach the urinary tract. (1) *Direct extension:* Organisms which are present in the anterior urethra normally in all individuals may migrate or be pushed by instruments into the urinary bladder. When bacteria are present in the bladder they may travel upstream into the renal pelvis despite the competency of the ureteral sphincters. There is good evidence that under certain conditions reflux of urine up the ureter takes place in some individuals. (2) *Hematogenous dissemination:* Organisms circulating in the blood may be deposited in the kidney. Experimentally, however, the intravenous injection of bacteria does not lead to the appearance of pyelonephritis unless obstruction to urine flow exists or unless the kidneys are slightly injured by massage. This suggests that some degree of urinary stasis or an underlying renal insult is necessary before bacteremia can produce infection. (3) *Lymphatic Spread:* Organisms may reach the kidney by way of lymphatic vessels of the urinary tract or from the bowel. When pyelonephritis is attributed to direct ascent of bacteria from the bladder, spread via lymphatics is probably also involved.

A great many organisms can be responsible for urinary tract infection, but the most common are: *E. coli*, *A. aerogenes*, Proteus strains, *Ps pyocyaneus*, and the paracolon group. Other gram-negative bacteria which are less frequently involved are: *H. influenzae*, the Friedlander bacillus (*K. pneumoniae*), dysentery bacilli, and Salmonellae. Some gram-positive cocci, primarily *Staph. aureus* or *albus*, and streptococci (mostly alpha- or non-hemolytic varieties, many

Some of these lesions are narrowed meatus, urethral stricture, bladder valves, malposition of the ureteral orifices, anomalous crossing of the ureters by blood vessels, narrowing of the uretero-pelvic junction, bifid pelvis, "double" kidney, or renal hypoplasia. (2) *Acquired Obstructive Defects:* These include urethral stricture, prostatic hypertrophy, hypertrophy of the vesical neck in females, stones, and tumors of the prostrate, urinary bladder, or kidney. (3) *Physiologic Obstruction:* Dilatation of the ureters during pregnancy due to the prolonged activity of high estrin levels allows stasis of the urine and predisposes to pyelonephritis. The elderly individual who is put to bed for a prolonged period may develop a urinary tract infection because the supine position does not permit complete emptying of the bladder. The administration of morphine, large quantities of codeine, or frequent doses of mercurial diuretic are sometimes responsible for urinary retention and subsequent infection. Neurologic disorders which produce malfunction of the bladder and chronic residual urine are also important. (4) *Instrumentation:* One of the most common factors contributing to bacterial invasion of the urinary tract is instrumentation. The passage of a catheter even once may introduce organisms and lead to cystitis, regardless of the care with which aseptic precautions are taken. Prolonged use of indwelling catheters of any type is accompanied by a high risk of pyelonephritis. There is a growing emphasis on the importance of this mechanism in the production of urinary tract infection. This whole problem has been highlighted by the recent reports on the frequency of asymptomatic kidney infections. (5) *Extra-Urinary Tract Infection:* Pyelonephritis may result from introduction of bacteria via the blood or lymphatic vessels. Thus, staphylococcal bacteremia may be the predisposing factor in multiple abscesses of the kidney, or miliary dissemination, the source of tuberculous pyelonephritis. Infection of the prostate with tubercle bacilli may be the focus from which infection of the renal tissues arises. Spread of

There are usually no constitutional manifestations. Laboratory examination generally reveals pyuria of varying degree and *Staph. albus*, *Staph. aureus*, and diphtheroid bacilli—organisms probably not causally related to the infection—in urethral cultures.

Some cases of non-specific urethritis occur as part of a more generalized picture called Reiter's syndrome—urethritis, arthritis, and conjunctivitis. In some instances there is an eruption on the soles of the feet resembling keratosis blenorrhagica, a lesion usually found in gonorrhea. Fever and other general symptoms of infection are present. The cause of Reiter's syndrome is unknown, although many cases have been associated with bacillary dysentery and are thought to represent hypersensitivity reactions. The diagnosis of nonspecific urethritis or Reiter's syndrome is made on the basis of the clinical picture only after gonorrhea, trichomonas infestation, chemical irritation, foreign body, and trauma have been ruled out.

Although the specific etiology is unknown, therapy of "non-specific" urethritis with antibiotic agents has been claimed to be successful. Terramycin (oxytetracycline) in a dose of 250 to 500 mg. orally 4 times daily for 5 days has been found to be effective. Aureomycin (chlortetracycline), in the same dose, is also thought to produce good results. A suggested alternate form of treatment with this drug is the intra-urethral instillation of a 0.25 per cent solution. This cannot be recommended since it produces severe irritation of the tissues.

Chronic Urethritis

The commonest cause of chronic urethritis is gonorrhea. However, chronic infection of the posterior urethra in females may be due to the organisms (*E. coli*, *A. aerogenes*, *Proteus*, etc.) which are often responsible for disease of other parts of the urinary tract. It has been suggested that this is the commonest disorder of the urinary tract in young

of which have the biological characteristics of enterococci) may be the causative agents. It is not uncommon to find two species of bacteria, usually one of the enteric organisms plus staphylococci or enterococci in some cases. Among the organisms which produce urinary tract disease uncommonly are *Actinomyces*, yeasts and fungi, the tubercle bacillus, *Filaria, Schistosoma japonicium,* and the typhoid bacillus. All strains of *Proteus* and many of *H. influenzae* are capable of splitting urea to form ammonia; infection with these organisms is featured by alkaline urine, calcareous bladder encrustation, and stone formation.

Urethritis

Acute Urethritis

Although many bacteria can be isolated from the urethra of patients with acute urethritis, they cannot, as a rule, be implicated as the causal factor since they are common components of the normal microflora of this area. These organisms include *Staph. albus., Staph. aureus,* and diphtheroids, *E. coli,* enterococci and other fecal species.

Acute urethritis is most often caused by the gonococcus; this is discussed in Chapter XII. *Trichomonas vaginalis* may also be responsible for urethritis and prostatitis. Most cases of acute inflammation of the urethra not due to gonorrhea fall into the category of "non-specific" urethritis, if trauma, foreign body, and chemical irritation can be ruled out. The etiology of this entity has not been determined; it has been suggested, but not proved, that it may be due to a virus. Many patients with "non-specific" urethritis have a history of recent venereal contact. The incubation period varies from 2 to 42 days with an average of 14 days. The outstanding manifestations are mucopurulent urethral discharge and dysuria; occasionally hematuria may be present. The symptoms in most cases usually persist for only 2 to 3 days, but they may last only one day or up to six years. There is often a tendency to remissions and exacerbations.

urinary tract. Organisms may reach the urinary bladder from the urethra as a result of instrumentation, from infected kidneys and ureters, by hematogenous or lymphatic spread, and through fistulae between the bladder and adjacent structures such as the vagina, rectum, colon, appendix, or open urachus. The factors which predispose to cystitis are (1) obstruction of any type at the vesical neck, (2) pregnancy, (3) residual urine because of a cystocele, operation, or mere prolonged bed rest in elderly individuals, (4) congenital or neurogenic atony of the detrusor muscle, and (5) the presence of calculi, foreign bodies, blood clots, and tumors, or diverticula in the bladder.

The symptoms of acute cystitis are frequency, dysuria, urgency and tenesmus; the most important signs are pyuria and bacilluria. Frequency is the most common manifestation in most cases; micturition may take place every few minutes. When the desire to void becomes imperative (urgency) and severe enough, incontinence may result. Dysuria varies in intensity and in some cases is the outstanding complaint. It may be only a mild burning sensation or sharp in character referred in the male to the perineum and the end of the penis Usually the pain is most intense throughout urination, although it may appear only at the beginning or the end. The urine contains an increased number of leucocytes, and bacteria are demonstrable in stained smears and cultures; infections in the urethra, periurethral spaces, glands of Littré, seminal vesicles, epididymis, or prostate may produce the same findings. Microscopic hematuria is frequent in acute cystitis, especially when stone, tumor, or tuberculosis of the bladder are present. Gross hematuria is the outstanding manifestation in some females, and when the disease is secondary to respiratory or systemic infections or coagulation defects. When fever of appreciable degree accompanies the other signs and symptoms, the possibility of pyelitis or pyelonephritis must be considered seriously because acute cystitis is usually not an isolated lesion.

girls and that it is too infrequently differentiated from cystitis and pyelonephritis. The syndrome is well-recognized by urologists as an entity in adults but has attracted only little interest in the child. The outstanding symptoms are urinary frequency and repeated episodes of fever, dysuria, and pyuria. Enuresis is often present. In some of the young patients, there is pain in the back, loin, or abdomen. The course is featured by repeated episodes of a syndrome consistent with pyelonephritis. X-ray study of the kidneys usually shows no obstruction or other abnormalities. Cystoscopic examination reveals hyperemia of the posterior third of the urethra and the bladder neck. The bladder itself is normal in appearance in early cases, but a granular mucosa and villus and polyp formation are seen in the more advanced ones. Severe fibrosis, stricture, chronic inflammatory changes *in the trigone, and urinary retention, are noted in women* but not in children. Voided urine contains a large number of leucocytes, but a catheterized specimen is strikingly free of cells in cases of posterior urethritis; this finding may be helpful in differentiating this disease from cystitis and pyelonephritis.

The treatment of chronic urethritis in adult females is primarily a urologic problem and consists of urethral dilatations, instillation of silver preparations or other bactericidal substances, and cauterization or electroresection. In young girls therapy includes urethral dilatation and the administration of antibiotic agents to which the organisms isolated from a carefully collected urine are susceptible. The antimicrobial drug should be administered in full dose for at least 10 to 12 days. Relapse occurs in about 25 per cent of cases despite treatment.

Cystitis

Cystitis is most frequently produced by the same bacteria which are responsible for infection in other parts of the

microscopically and bacteriologically in order to detect relapse as early as possible. When recurrence of infection is noted, re-treatment with an appropriate drug should be initiated promptly.

Pyelonephritis

The organisms responsible for acute and chronic pyelonephritis are most commonly the gram negative bacilli (*E. coli*, *Proteus*, and *Pseudomonas pyocyaneus*) and gram positive cocci (*Staph. aureus* and enterococci). A variety of other bacteria including *H. influenzae*, *K. pneumoniae* (Friedlander bacillus), dysentery bacilli, *A. aerogenes* and *Salmonella* may be the causative agents. In not a small number of cases both a gram-negative bacillus and a gram-positive coccus are involved, *E. coli* and *Staph. aureus* being the commonest pair. *Proteus*, *Pseudomonas*, and enterococci are more frequently present in chronic and anatomically complicated urinary tract infections than in uncomplicated ones. Enterococci are commonly encountered in females who become infected after catheterization.

The symptoms and signs of pyelonephritis are quite variable. In the acute form or in severe exacerbations of the chronic disease, the onset is heralded by high grade fever, leucocytosis, and other manifestations of urinary tract involvement. On the other hand, patients may have only mild elevation of temperature with very few symptoms. The classic features of simple acute pyelonephritis are chills, fever, frequency, urgency, dysuria, low back pain, and costovertebral angle tenderness. Symptoms referable to the lower urinary tract are common; this indicates the great frequency with which cystitis accompanies infection of the kidneys. As pointed out above, it is questionable whether "pure" cystitis or pyelitis occurs without renal involvement.

A special form of acute pyelonephritis, acute necrotizing renal papillitis, may develop in the course of chronic renal

The diagnosis of acute cystitis is usually suspected when frequency, dysuria, and pyuria are present. The etiology can be determined only by isolation and identification of the organisms from the urine. Specimens obtained by the "clean catch" method or, in some instances, by sterile catheterization, must be studied; the number of bacteria must be determined to rule out contamination (see Pg. 399). It is imperative that all cases of cystitis be thoroughly investigated for the presence of any lesions that may predispose to its development. The possibility of pyelonephritis must always be considered. Intravenous or retrograde pyelography, cystoscopy, and even renal biopsy are very valuable procedures and should be carried out in some instances, especially when the disease is recurrent.

Treatment of acute cystitis consists of elimination, if possible, of all predisposing factors; this may necessitate surgical intervention in cases in which obstruction, tumors, or stones are present. Antimicrobial therapy is indicated, in addition. The most effective drug should be selected on the basis of sensitivity tests of the isolated organisms and given in maximal doses for a period of 12 to 14 days. Until the results of sensitivity testing become available in some cases, and even as the final definitive therapy in others, sulfonamide treatment may be very effective. These agents must be used in full doses, since the problem is one of treating the infected bladder tissue and not a "contaminated" or "infected" urine. Sulfadiazine (4 gms. initially followed by one gram every 4 hours), Gantrisin (same quantity), or Kynex (sulfamethoxy pyridazine—2 gms. initially followed by a single gram each day) have been employed with good results. Unfortunately, many of the strains of bacteria isolated from cases of acute cystitis are resistant to all sulfonamides; in such instances, the antibiotic to which they are susceptible *in vitro* should be administered. After the prescribed course of therapy has been completed, patients should be seen at weekly intervals for 1 to 2 months and their urine studied

addition, the factors which favor recurrence are seldom overcome by the routine management of the acute attack. For this reason, the danger of chronicity and the possibility of subsequent renal insufficiency increase with each episode. The signs, symptoms, and laboratory findings in recurrent acute pyelonephritis are the same as those in the primary disease. The diagnosis of a recurrence is based on a history or presence of evidence of prior renal infection.

Chronic pyelonephritis may present itself in one of four forms: (1) Asymptomatic with no manifestations, or only pyuria or a significant degree of bacilluria, or both; (2) Chronic renal disease with acute exacerbations characterized by the syndromes described above; (3) Progressive renal failure, (4) Persistent and progressive decrease in kidney function associated with hypertension which is usually severe and not infrequently of the malignant type and associated with retinal changes such as venous engorgement, arteriolar spasm, arteriovenous "nicking", hemorrhages, and exudates. The presence of chronic pyelonephritis in most patients is not suspected until impairment of renal efficiency or injury to the cadiovascular system brings them to the attention of a physician. Even then, the kidney lesion is often not diagnosed unless pyuria is detected. Many such individuals, however, do not have an increased number of white cells in their urine so that the disease is completely overlooked unless special bacteriologic studies are carried out.

The frequency and importance of chronic pyelonephritis cannot be overstressed This has recently been clearly demonstrated in a study which revealed that 5 per cent of males and 20 per cent of all diabetics visiting the outpatient department of a large city hospital have asymptomatic pyelonephritis as proved by the isolation of large numbers of pathogenic bacteria from their urine. In many instances there was no significant pyuria The paucity or total absence of symptoms of urinary tract infection and the relative difficulty of eradicating the causative organisms even when

infection in diabetics and in individuals with urinary tract obstruction produced by prostatic hypertrophy; it occurs rarely in healthy persons. This disease comprises 25 per cent of all cases of pyelonephritis in patients with diabetes mellitus in whom it is four times more common a cause of death than simple pyelonephritis. In one group of diabetics acute necortizing papillitis was found to be the sixth most frequent cause of death. The renal lesions are usually bilateral and symmetrical; they are infarct-like necrosis of the tips of all of the pyramids and may be associated with cortical abscesses. The causative organism is most frequently *Staph. aureus* although other bacteria, *Proteus* strains, for example, may be the inciting agents. Fever is of high degree, chills are common, severe back pain and costovertebral angle tenderness are frequent, and oliguria and anuria may supervene. The urine contains bacteria, leucocytes in large number, "pus casts", and many renal papillary cells. If not recognized, or if not amenable to specific antimicrobial therapy, the disease may terminate in death by the third or fourth day, since rapidly progressing uremia is the rule. The presence of acute necrotizing renal papillitis is suspected in the following situations: (1) in any patient with sepsis in whom symptoms of urinary tract disease appear suddenly, (2) in any case in which nitrogen retention and coma develop rapidly in the absence of antecedent pyelonephritis, (3) in individuals in whom there is a sudden exacerbation of a low-grade nephritis, (4) in any known diabetic who develops severe pyelonephritis, and (5) in instances of severe diabetic acidosis which respond to treatment for the acidotic state but in which progressive stupor and azotemia appear in the absence of shock or known renal tubular damage.

Recurrences are frequent in pyelonephritis. They are often associated with incomplete healing of the renal process but may occur when the infection has been eradicated. Their frequency and severity are unpredictable and variable. Each acute episode, however, destroys more kidney tissue. In

urinary tract infection is, as a rule, not present. If, however, bacteria are readily apparent, the diagnosis of pyelonephritis is strongly suggested. Both colony counts and stained smears of urine may yield false positive results if the specimen, although properly collected, is permitted to sit at room temperature (equivalent to incubation at 28° C or so) for several hours before either of these procedures is carried out because the organisms multiply. The tests must be performed immediately, or the urine stored temporarily (no more than 12 hours) in a cold refrigerator until they can be done.

In addition to study of the urine, every case of suspected urinary tract infection must be subjected to a number of other diagnostic investigations. Prognosis may be partially estimated from chemical determinations of renal function (blood urea nitrogen, carbon dioxide content, creatinine, sodium, potassium, and chloride) as well as various urine concentration tests and PSP excretion. The status of the cardiovascular system must also be ascertained. Pyelography is indicated in most instances because it may reveal (a) calyceal distortions consistent with chronic pyelonephritis, (b) anatomic defects important in the initiation and persistence of the disease, and (c) the functional capacity of the kidney based on the relative rate of excretion of the injected dye. In most instances, intravenous pyelography is the preferred procedure; retrograde studies are indicated in special instances. It must be stressed that these procedures are not always diagnostic. In acute and even in chronic pyelonephritis, the pyelogram may be normal. That x-ray examination of the kidneys may fail to reveal the presence of infection has been clearly demonstrated by biopsy studies; these may show anatomical and bacteriological evidence of pyelonephritis in patients in whom the pyelogram appears normal. Renal biopsy is a very important diagnostic aid and, when carried out *carefully by experienced personnel*, is without danger. Even this diagnostic procedure is not

potent antimicrobial agents are used combine to make this one of the most difficult diagnostic and therapeutic problems in medicine.

In acute episodes of pyelonephritis, the urine contains many leucocytes some of which are clumped, white blood cell casts, red blood cells, albumin, and usually a large number of bacteria. Urine is best collected by the "clean catch" method, making certain that the external genitalia have been scrupulously cleansed and collecting only the last 10 ml. of urine voided. It has been presumed that this procedure cannot be used in females because of the ease with which bacterial contamination from the vulva takes place, and that the only method of collecting urine for culture is by catheterization. This is not true. While single catheterizations are not highly dangerous, they occasionally result in the accidental introduction of bacteria into the bladder and produce infection especially in diabetic patients and those with chronic urinary tract obstruction. In the writer's opinion, catheterization must be avoided whenever possible. The number of bacteria in a properly collected "clean catch" urine is decisive, within certain limits, in determining whether the organisms which are present represent contamination or infection.

Determination of the number of bacteria in the urine is an invaluable procedure and must be carried out in all suspected cases of pyelonephritis whether or not pyuria is detected. Although there is some disagreement as to the exact level below which infection can be ruled out (1,000 to 10,000 organisms per ml. have been proposed) there is usually little or no difficulty in reaching a conclusion because 1,000,000 or more bacteria per ml are present in most cases of pyelonephritis. The writer has adopted the practice of considering 10,000 organisms or less per ml. of urine as indicative of contamination.

Gram-stained smears of fresh undiluted urine are also helpful. If no organisms are detected by this procedure,

ble. Wherever possible, it is best to use bactericidal rather than bacteriostatic antibiotics. Treatment should be continued for 2 weeks. Recurrence may require the use of a different drug.

Staph. aureus or *Proteus* strains produce acute necrotizing papillitis most often. A gram stain of the urine will quickly reveal whether gram-positive cocci or gram-negative rods are present. If the former are detected, therapy with 0.5 gm. of chloramphenicol plus 0.5 gm. of erythromycin every 6 hours (either orally or parenterally) should be initiated. If gram-negative rods are observed, chloramphenicol in the same dose may be effective. The final choice of antimicrobial agent, however, depends on the results of sensitivity tests of the isolated organisms to various drugs. Some strains of *Proteus* are very suceptible to novobiocin (Cathomycin, Albamycin). In this fulminating type of pyelonephritis, it is well to keep in mind that death may occur rapidly; for this reason selection of the antibiotic must be quick and critical and the schedule of treatment intensive

All patients with bacterial disease of the urinary tract should be studied by means of intravenous or, when indicated, retrograde pyelography to detect congenital or acquired obstructive defects which may be predisposing to recurrent or chronic infection. Cystoscopy may be necessary in some instances. Whenever feasible, any lesions which impede the normal flow of urine should be removed after the acute infectious process has been brought under control.

The management of chronic pyelonephritis is generally disappointing. Although drugs may be administered which, on the basis of sensitivity studies, should produce eradication of the offending organisms, ultimate bacteriologic control occurs in no greater than 10 per cent of cases. The writer has tried one approach to this problem which has been successful in 2 cases. Patients with chronic pyelonephritis in whom acute exacerbations had occurred were treated for 2 weeks with large doses of the antibiotic

always reliable, however, since the specimen may by chance be obtained from a normal area of the kidney.

The diagnosis of acute pyelonephritis in which symptoms and signs appear is relatively simple. The general manifestations of infection together with frequency, urgency, dysuria, flank or back pain, and costovertebral angle tenderness are pathognomonic. A previous history of renal infection should lead the physician to consider the kidney as the site of disease in any individual with unexplained fever. The picture of necrotizing renal papillitis is so striking that its presence is frequently suspected when it develops in patients with diabetes mellitus or chronic urinary tract obstruction.

Examination of the urine is the most important diagnostic procedure. Although, as pointed out above, increased numbers of white cells can be demonstrated in many cases, the urine may be completely normal when chronic renal infection is present. This must not mislead the physician, however, because progressive kidney failure and vascular disease may be taking place in the face of an apparently normal urine. The only method of establishing the diagnosis of pyelonephritis in such cases is by quantitative study of the urine. "Glitter cells," polymorphonuclear leucocytes, the granules of which exhibit active Brownian movement, are thought to be diagnostic of renal infection when detected in the urine; this is questionable.

The treatment of kidney infection is relatively difficult and involves several approaches Since most instances of simple acute pyelonephritis with fever and chills are due to gram-negative bacilli or *Staph. aureus*, it is best to initiate therapy with chloramphenicol in a dose of 0.5 gm. orally every 6 hours. Some physicians prefer sulfadiazine or Gantrisin (4 gms. to start followed by one gram every 4 hours). The causative organism must be isolated from the urine and tested for sensitivity to various antibiotics as rapidly as possible in every case. Treatment should be changed to the agent to which the bacteria are found to be most suscepti-

a nurse, attendant, or physician close by, may be all that is necessary to overcome his retention. Occasionally, when these measures are unsuccessful, micturition may be reflexly stimulated by having the patient expel a warm, bland enema in the natural sitting position on a commode. In some instances, *the use of furmethide or urecholine for a short* period is very helpful. In certain situations, an inlying catheter must be inserted and left in the bladder for a variable period of time (poliomyelitis, multiple sclerosis, and certain operations on the urogenital tract). Infection accompanies this procedure in the great majority of cases and cannot be prevented by the use of sulfonamides or antibiotics, or even by the simultaneous application of tidal drainage and antimicrobial drugs. The writer's experience in the prophylaxis of urinary tract infections in poliomyelitis patients with paralyzed bladders requiring a Foley catheter has been very discouraging, regardless of the use of all types of antimicrobial drugs and all varieties of tidal drainage. Approximately two-thirds of such patients have developed pyelonephritis which has been difficult or impossible to eradicate.

Tuberculous Pyelonephritis

The kidney is the most frequent site of tuberculosis involving the urinary tract. Tuberculous pyelonephritis is more common in adults than in children and occurs much more frequently in males, in whom it is often secondary to tuberculosis of the genitalia. Not all patients have evidence of an active pulmonary lesion.

The early stages of renal tuberculosis are symptomless and the lesion may remain clinically latent for a long while. Since the bacilli from the involved kidney are conveyed to the bladder in the urine, cystitis is very frequent and accounts for most of the symptoms—dysuria, frequency, and urgency—which are indistinguishable from those produced

selected on the basis of sensitivity tests, and then given sulfadiazine or gantrisin (1 gm. twice a day) continously *thereafter.* In two instances, sulfonamide therapy has been maintained for 3 years; there has not been an exacerbation of symptoms, pyuria is not present, and bacterial counts of the urine have revealed only a small number of organisms in both cases. This method of treatment cannot be recommended for general use at present until its merit has been proved or disproved by a broad experience. Difficulty in the management of some instances of chronic pyelonephritis is due to the fact that more than one species of bacteria is involved and that, in many instances, the organisms are totally resistant to all of the available antimicrobial agents. In some of these cases, the physician must resort to giving methanamine (Urotropin) or mandelamine in order to suppress, if only a little, the infectious process in the kidneys. All patients with chronic pyelonephritis should be evaluated periodically for their general vascular status and renal function so that any measures which may delay the inexorable progression of renal-vascular disease may be instituted.

One of the most important aspects of the problem of pyelonephritis is its prevention. Since evidence is overwhelming that many cases of chronic infection of the urinary tract are directly due to catheterization, no matter how carefully carried out, one obvious prophylaxis for the disease is avoidance of passing catheters or other instruments into the urinary bladder when their use is not absolutely required. Although single catheterizations are associated less frequently with the initiation of pyelonephritis, they still constitute some source of danger. For this reason, individuals should be encouraged to void when suffering from transient episodes of urinary retention. Permitting a patient to stand beside his bed or sit on a commode, applying warm moist towels to his lower abdomen, running water in a sink for him to hear, and allowing him to try to pass urine without

treatment produces little response, the possibility of nephrectomy should be considered. This is generally performed only if the main brunt of damage involves a single kidney, as shown by pyelography and differential function studies.

Renal Carbuncle and Perinephric Abscess

Organisms which invade the kidney may produce a localized area of suppuration. The source is usually a bacteremia. The only manifestations are fever, chills, and leucocytosis. There are usually no signs indicating the site of infection. As a rule, the presence of renal carbuncle is not suspected until it ruptures into the pelvis to load the urine with pus cells and bacteria, or until it penetrates outward to produce a perinephric abscess. In the former instance, the initial diagnosis is usually pyelonephritis with the conjecture of a unilateral ureteral block temporarily released to allow the entry of exudate into the urine. The presence of perinephric abscess cannot be detected early, the process presenting only as an obscure fever with leucocytosis. After 1 to 2 weeks, however, bulging in the flank or back on the involved side often becomes apparent. X-ray of the abdomen reveals unilateral obliteration of the psoas shadow; this may be detected in some instances before a mass is palpable.

The medical treatment of renal carbuncle is usually the same as for acute pyelonephritis, the choice of drug depending on the nature and sensitivity of the responsible organism (often *Staph. aureus*). If precise bacteriological data are not available, it is probably best to give large doses of crystalline penicillin G (2,000,000 to 4,000,000 units in divided doses intramuscularly per day) or a combination of 0.5 gm. each of erythromycin and chloramphenicol every 6 hours, orally or parenterally. The chemotherapy of perinephric abscess is the same. Surgical consultation is necessary in all cases because, in some, final cure can be effected only by incision and drainage.

by other types of bladder infection. Later in the course of the disease, often when the kidneys are the site of extensive caseous necrosis, cavitation, and excavation, there may be some flank discomfort or mild costovertebral angle tenderness. Constitutional reaction, if present, is usually slight. Examination of the urine reveals, as a rule, hematuria, pyuria, and albuminuria of varying degree; any of these abnormalities may be present alone.

The diagnosis of tuberculous pyelonephritis should be suspected in any patient with a pulmonary lesion, urinary tract symptoms, or abnormal urine from which organisms cannot be recovered by the usual methods of culture. The disease must also be considered in any case of unexplained dysuria, hematuria, pyuria, albuminuria, or any combination of these abnormalities. Pyelography, cystoscopy, and possibly ureteral catheterization are indicated in all such instances. The diagnosis is confirmed by isolation of tubercle bacilli from urine cultured in appropriate media and inoculated into guinea pigs. Acid-fast stains of urine may be misleading because of confusion with the smegma bacillus (*M. smegmatis*), an acid-fast organism commonly present on the external genitalia.

The treatment of tuberculosis of the kidney is the same as that used when the lungs are involved. The administration of 1 gm. of streptomycin intramuscularly twice a week plus 10 to 12 gms. of para-aminosalicylic acid orally per day has proved curative in many cases when continued for a full year. The same quantity of streptomycin given together with isonicotinic acid hydrazide (8 to 10 mg. per Kg. of body weight), is also highly effective. Unless they are very ill, patients may be permitted at first to continue their usual occupation on a half-time basis, providing they do not carry out strenuous physical activity and do not have an open pulmonary lesion. After 3 to 6 months, they are allowed more activity. In cases in which renal tuberculosis is far advanced at the time therapy is initiated and

ing and fluctuation of the gland which feels hard when the capsule is under severe *tension. The abscess may rupture* into the urethra; this is accompanied by a discharge of pus and blood. Recurrences of prostatic infection may develop in patients who have had a prostatic abscess. Acute gonococcal prostatitis is frequently associated with seminal vesiculitis and epididymitis, but either of these may complicate acute infections of the prostate due to other organisms

The *chronic stage of gonorrhea may be symptomless;* however, there may be a small amount of mucoid urethral discharge in the morning (gleet) or urgency and frequency of urination. In a small number of patients, chronic prostatitis may develop and persist for a long time without giving rise to symptoms. When manifestations are present, they include backache, persistent discomfort or a feeling of fullness in the perineum, urinary frequency, recurrent nocturnal emissions, pain and burning along the course of the urethra (*referred at times to* the *glans penis*), and occasionally pain and burning in the urethra during coitus and after ejaculation. The prostate feels soft in the mild cases, and hard and irregular in the more advanced ones. Prostatic massage yields fluid which contains a large number of leucocytes. It must be emphasized that other organisms, usually those responsible for urinary tract infection or epididymitis, are responsible for chronic prostatitis more frequently than the gonococcus. Treatment must be selected on the basis of the nature and sensitivity of the organisms isolated from the prostatic secretions.

Gonorrhea and Other Infections of the Genitalia in the Female

Gonorrhea in the female often begins, as in the male, with acute urethritis which produces dysuria, frequency and a purulent exudate. Cervicitis may be present at the same time and be responsible *for a profuse vaginal discharge*. The disease may spread to Skene's and the Bartholin glands and

CHAPTER XII

GENITO-INFECTIOUS DISEASES

GONORRHEA AND OTHER ACUTE PYOGENIC INFECTIONS OF THE GENITALIA

Gonorrhea in the Male

The incubation period of gonorrhea is 3 to 5 days. The initial lesion of the disease in the male is acute anterior urethritis. This is characterized by a purulent urethral discharge and burning on urination. When diagnosed and treated early, the disease is brought to an abrupt halt. Without treatment, spread of infection takes place locally at first and then may become disseminated with distant foci.

Acute prostatitis may follow the anterior urethritis of gonorrhea. Urinary retention, fever, and a sensation of fullness in the rectum are the common manifestations. In some cases, chills and fever are the only symptoms. Palpation of the prostate reveals it to be enlarged, tense, and tender. Prostatic fluid obtained by massage contains numerous leucocytes and the characteristic gram-negative, biscuit-shaped diplococci. Acute prostatitis may be due to organisms other than the gonococcus. The etiology is not distinguishable on clinical grounds alone; it can be established only by bacteriologic study. Gram-negative organisms (*E. coli, Proteus*) and pyogenic cocci (*Staph. aureus*) may be the causative agents. Rarely, prostatic abscess follows gonorrhea; it is produced more frequently by other bacteria. In these cases, there is fever and eventual soften-

infection may be suspected on the basis of the appearance of the vaginal discharge; it is confirmed by demonstration of the parasities in a hanging drop preparation of the vaginal fluid. In other types, the etiology is established by isolation of the causative organisms. Saboraud's medium should always be used in order that *Candida* may not be overlooked. *Monilia* vaginitis in non-pregnant patients must be investigated from the standpoint of diabetes mellitus, since it may be the first departure from health noted by the female diabetic.

Acute pelvic inflammatory disease may result from extension of infection from the cervix and is due to the gonococcus in about 60 per cent of cases; the remainder are produced by anaerobic or aerobic streptococci or by *Staph. aureus* and frequently follow puerperal or post-abortal infections. Acute gonococcal pelvic inflammatory disease may be an immediate sequel of gonorrhea or may occur months or even years after the primary infection. The main impact of the gonococcus is on the mucosa of the Fallopian tube; this becomes reddened and swollen and is covered by a purulent exudate which may escape into the peritoneal space to produce pelvic abscesses, oophoritis, or acute peritonitis Adhesions and scarring occur and lead to pyosalpinx and sterility. When staphylococci or streptococci are the agents responsible for acute salpingitis, the organisms reach the tubes by way of the veins and lymphatics of the broad ligaments, resulting thrombophlebitis, periphlebitis, lymphangitis, and perilymphangitis with cellulitis, and even abscess of the broad ligaments are frequent. Although the walls of the tubes are thickened, the lumina are patent and nearly normal in diameter; this is the reason that sterility is much less frequent after staphylococcal or streptococcal than after gonococcal infection. The symptoms and signs of acute pelvic inflammatory disease are the same regardless of the nature of the organism which produces it and consist of fever, often of high degree, chills, nausea and vomiting,

become chronic. Not all Bartholin abscesses are, however, due to the gonococcus; *Staph. aureus* and gram-negative organisms of the enteric group produce infection in these glands more commonly than does the gonococcus. The infected organ is turgid, swollen, and painful, and purulent exudate can be expressed from the duct opening. The overlying skin is red and tender. There is usually some degree of fever, and walking may be difficult because it produces pain.

In the prepubertal child and occasionally in post-menopausal adults, the picture produced by gonococcal invasion is acute vulvovaginitis, a lesion which rarely, if ever, is seen in the menstruating female. The vulva is red and edematous, the vaginal walls are markedly inflamed, and there is a profuse, creamy, vaginal discharge which contains the gonococcus, usually in large numbers.

In menstruating women, *Trichomonas* and *Candida* (*Monilia*) produce vaginal infection most often. With trichomonas vaginitis which is frequently contracted from the sexual partner (the organisms are present in the prostate), the mucous membrane is reddened and the posterior fornix often presents the almost pathognomonic strawberry-like appearance. Small erosions may be present on the cervix. The discharge may be thin and milky but is often very thick, white, or yellow-white, and has a "foamy" or "bubbly" appearance. Dyspareunia is common. In mycotic vaginitis (*Monilia*), most common during pregnancy, the vulva is reddened, edematous and sometimes the site of thrush-like patches on the surface; the outstanding symptoms are itching and burning. The entire vagina is reddened and a copious, thin to thick, white, highly acid discharge is present. Other organisms which may produce acute vaginitis are the beta-hemolytic streptococcus, *Staph. aureus*, and *E. coli;* the latter has been isolated only from post-menopausal women. The signs and symptoms are similar to those present with other infections in this area. The diagnosis of *Trichomonas*

detected over the liver. Small pleural effusions may infrequently develop on the side of the lesion. The disease usually subsides in 1 to 4 weeks, even without specific therapy, but leads to the formation of "violin string" adhesions within the abdomen.

Mono- or polyarthritis, migratory in character and involving primarily the larger joints, may occur at any time during the course of gonorrhea. Tenosynovitis, especially of the wrists, dorsum of the hands and feet and in the areas of the internal and external malleoli, is a frequent accompaniment of the joint involvement and helps to distinguish gonococcal from other types of arthritis. Purulent conjunctivitis may be present at the same time. In patients with urethritis, conjunctivitis and polyarthritis, there may be confusion with Reiter's syndrome, a disease of unknown etiology, differentiation can be made on the basis of positive bacteriologic and serologic evidence for gonococcal infection. A rare complication of gonorrhea is a sharply demarcated thickening of the skin which may become necrotic on the soles of the feet, this is keratosis blenorrhagica and has also been observed in Reiter's syndrome

When the gonococcus invades the blood stream, it may produce focal infection in various organs Acute purulent meningitis, indistinguishable from that produced by the meningococcus and other bacteria may appear and can be differentiated only by microbiological studies Metastatic lesions may occur in almost any tissues. Acute endocarditis may develop, the aortic valve being affected most frequently Involvement of the right side of the heart is more frequent with gonococcal than with other types of endocarditis. A common feature of this disease is a daily double spike of fever.

The presumptive diagnosis of acute gonorrhea is made by demonstration of typical biscuit-shaped gram-negative diplococci, many of which are situated intracellularly, in

pelvic and lower abdominal pain, abdominal distension, rigidity of the abdominal muscles, and extreme tenderness of the adnexa. Pelvic examination in the acute stage reveals pain on attempted movement of the uterus which is usually fixed. When this subsides, a small indefinite mass adherent to the ovary can often be detected. The presence of a complicating pelvic abscess is suspected if fever and pelvic pain persist, and examination discloses fluctuation in the cul-de-sac, the sides of the pelvis, or along the posterior vaginal wall.

Chronic pelvic inflammatory disease with endometritis and salpingitis may follow gonococcal infections or those produced by other organisms. Pyosalpinx is usually the result of gonorrhea; the organisms often disappear within a short time of the development of this lesion so that the contents of the occluded portion of the tube are sterile. The signs and symptoms of chronic pelvic inflammatory disease are: (1) severe, moderate, or mild pain (often described as a bearing down or aching discomfort in the lower abdomen or pelvis) which is exaggerated just before or during menstruation, (2) backache, (3) rectal discomfort, (4) changes in menstrual rhythm, (5) menorrhagia or metrorrhagia, (6) vaginal discharge, (7) sterility, (8) bladder irritability, and (9) tender, irregular and fixed mass on both sides of the pelvis or filling the cul-de-sac.

Extra-Genital Complications of Gonorrhea

An infrequent complication of gonorrhea in the female is perihepatitis, peritonitis involving the upper abdomen. This is known as the Curtis-Fitzhugh syndrome and may develop as late as 5 years after acute gonococcal urethritis. It is usually heralded by the sudden onset of sharp upper abdominal pain which may be referred to the right shoulder or exaggerated by coughing or deep breathing. A moderate degree of fever is common. A friction rub is occasionally

Syphilis

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The incubation period of the primary lesion of syphilis, the chancre, varies from 10 to 90 days. It appears at the site of inoculation of the spirochetes usually about 3 to 6 weeks after exposure and consists of a *solitary, indurated, nonpainful* ulcer which is often accompanied by painless enlargement of the regional lymph nodes (satellite bubo) and which heals slowly with scar formation. Multiple, small, and even painful chancres may develop and cause diagnostic confusion. The lesion is on or near the genitalia in 95 per cent of cases In the male, it most often appears on the prepuce or coronal sulcus; it may involve the glans, penile shaft, pubis, scrotum, or be intraurethral in location. In the female, it is most commonly found on the labia or in the fourchette; it may also be present on the cervix, perineum, pubis, clitoris, or in the urethra. Multiple chancres are not rare in women. About 5 per cent of the primary lesions of syphilis occur on the lips, mouth, or female breast.

The *secondary stage of syphilis* usually appears about 6 weeks after the primary lesion. In some patients it develops without a detectable preceding chancre, in others, it is entirely absent. The skin lesions of secondary syphilis are very variable in morphology and may be confused with a number of other diseases. Papular, maculopapular, pustular, annular, and follicular eruptions may appear; vesicles, however, are never present. The rash is commonly widespread, and frequently involves the palms, soles, and face in addition to the rest of the body and is sometimes pruritic. The mouth is often involved. Painless, superficial ulcers are

gram-stained smears. However, since non-pathogenic *Neisseria* are very frequently present on the genitalia and cannot be distinguished from the gonococcus morphologically, discharges should always be cultured and the organisms isolated and identified by a positive oxidase test and sugar fermentation reactions. In cases of arthritis or other accessible focal lesions, every attempt should be made to recover the bacteria. Blood cultures must always be obtained when disseminated infection is suspected or when the possibility of endocarditis is considered. All cultures should be incubated in an atmosphere of 10 per cent carbon dioxide. In obscure cases, complement fixation tests for the gonococcus may be of value.

Penicillin is the drug of choice for the treatment of all types of gonococcal infection. A single injection of 300,000 units of procaine penicillin cures most acute cases; if the disease persists after 3 to 4 days, another injection of the same quantity is indicated. A watery urethral discharge may be noted in as many as 20 per cent of males even after the organisms have been eradicated. In more deep-seated and in chronic gonococcal disease, the same dose of penicillin should be administered for 7 to 10 days. When serious systemic involvement such as acute endocarditis is present, aqueous benzyl penicillin G must be employed; the dose and duration of therapy are the same as for other forms of acute valvular infection (Chapter VIII). All cases of gonococcal infection, whether acute or chronic, should be studied for the possibility of syphilis by repeated serologic tests.

Acute gonorrhea is easily preventable. The administration of a single dose of 250,000 units of crystalline penicillin G orally within 2 to 3 hours after venereal contact will prevent the development of the disease in practically all instances. Such prophylaxis is, however, probably not effective against syphilis; patients given this kind of protection must be followed carefully for some time to rule out the presence of luetic infection.

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present on the buccal surfaces, tongue, and inner aspects of the lips; these are covered by a thin, grayish exudate which contains large numbers of spirochetes and are known as "mucous patches". Erosions may appear at the palpebral fissures (split papules) and be mistaken for perlèche or riboflavin deficiency. Broad, flat, wart-like lesions—condylomata—are found on the labia majora, perineum, and anal regions; these are highly infectious.

Other manifestations which are present in secondary syphilis are malaise, lassitude, headache, fever, myalgia, and generalized lymphadenopathy; the nodes are usually quite large and not tender. The spleen is sometimes palpable. Alopecia may be striking. Iritis and neuroretinitis with blurring and hyperemia of the optic nerve head and retinal edema appear in a small number of cases. Skeletal lesions develop in some instances; the tibia, skull, and sternoclavicular joints are most often affected and are the site of localized areas of swelling and tenderness. X-ray in these cases reveals periostitis or destructive lesions of the bone. Arthralgia and hydrarthrosis are occasionally present. Acute nephrosis with proteinuria, edema, and hypercholesterolemia may occur. Central nervous system involvement with meningitis or cranial nerve palsies takes place in some patients. The serologic test for syphilis is positive in 100 per cent of cases in this stage of the disease.

The primary and secondary stages of syphilis when skin and mucous membrane lesions are present are the most infectious periods. Genital condylomata and oral mucous membrane lesions are very contagious. Milk, tears, saliva and semen are not nearly so dangerous. The blood of patients in these stages of lues may contain spirochetes and should never be used for transfusion, this is true even during the incubation period at the time when seropositivity has not yet developed. The risk of transmitting syphilis by direct contact or blood transfusion is greatest in the first 4 years after acquiring infection; it is negligible after this.

The disease can be transmitted to the fetus for as long as 10 years after it is acquired; this occurs most often, however, during the first 4 years.

Latent Syphilis

The latent stage of syphilis is the phase in which there are no clinical signs or symptoms. One-third of patients cannot recall a primary lesion or secondary manifestations. The diagnosis in this stage is made entirely on the demonstration of a positive serologic test. Most cases of latent lues have developed sufficient resistance to prevent late clinical manifestations from appearing Approximately 75 per cent will remain latent even in the absence of specific therapy.

Many organs and tissues may be involved during the *spirochetemia* which characterizes the early phases of syphilis but may not show evidence of dysfunction until many years later. The skin may be the site of small nodular lesions or ulcerating gummas. The latter start as painless subcutaneous tumors which gradually soften and rupture; the former are slightly raised, reddish brown lesions which often coalesce to form serpiginous lesions. Gummas may also be present on the mucous membranes of the nose and throat where they produce pain and destruction of the hard palate and nasal septum.

The bones are often involved during the latent stage of syphilis Periostitis is the commonest lesion, it is observed in the skull and tibia most frequently, and in the clavicles, humerus, ribs, and nasopalatine structures less often. Osteolytic lesions may be present in the skull. The development of the so-called Charcot joint is due to destruction of proprioceptive nerves in tabes dorsalis; usually a single weight-bearing joint is affected such as the knee, ankle, hip, and occasionally the spine.

The gastrointestinal tract is involved in some cases of latent lues. Small or large gummas of the liver have been observed; hepar lobatum follows healing. The stomach is

rarely affected; there is diffuse granulomatous infiltration leading to annular constriction, ulceration, and obstruction in the area of the pylorus. Involvement of other parts of the intestinal tract is exceedingly uncommon. Gummas may develop on the vocal cords and be responsible for ulcer formation. Rarely the trachea, bronchi, lungs, or mediastinal lymph nodes may be the sites of syphilitic infection. Interstitial nephritis is seen occasionally; gummas of the kidney are very rare.

Involvement of the heart and aorta accounts for the majority of deaths in syphilis. Cardiovascular lues is more common in men than in women and in Negroes than in white patients. The manifestations usually appear 20 to 30 years after infection. The commonest lesions are (1) dilatation of the aortic ring producing aortic insufficiency and progressive heart failure, and (2) aneurysm of the aorta. The coronary arteries may be involved. Gumma of the myocardium has been noted, and it has been suggested that syphilitic myocarditis may also occur. The reader is referred to any authoritative textbook on heart disease for a complete description of the cardiovascular manifestations of syphilis.

Together with cardiovascular lues, involvement of the central nervous system accounts for 90 per cent of the deaths from syphilis. Only about 10 to 15 per cent of patients develop nervous system manifestations; these are discussed in detail in Chapter XIII.

Infection of the fetus usually occurs after the fifth month of pregnancy in syphilitic women. It takes place most often when early untreated lues is present in the mother, although it is sometimes observed even when she is in the latent stage. The pregnancy may terminate in stillbirth, premature delivery, or the birth of an infected child. The maternal disease becomes attenuated as its duration is prolonged and the possibility of fetal infection decreases with each succeeding pregnancy. The gravid state may have a beneficial

effect on syphilis; late manifestations are less common in multiparous women. The lesions of early lues may be suppressed.

Infection of the fetus leads to congenital syphilis which is often an overwhelming infection. The infants are severely ill, undernourished, and dehydrated. The most common lesions involve the skin and consist of fissures, condylomata and bullae. Persistent rhinitis, tenderness over the long bones, and pseudoparalysis are common. In late congenital syphilis (second decade of life), signs of central nervous system involvement may appear. Nerve deafness, optic atrophy, or paresis are the outstanding findings; the prognosis of these lesions is serious. Cardiovascular involvement is very rare. The typical late stigmata are Hutchinson teeth, frontal bossing, high arched palate, saber shins, "mulberry" first molar teeth, interstitial keratitis, deafness, and occasionally hydrarthrosis of the knee joints (Chitton's synovitis).

The diagnosis of syphilis depends on (1) detection of the characteristic primary lesion or the manifestations of the secondary stage of the disease, (2) demonstration of spirochetes by dark-field examination of lesions, and (3) the presence of a positive serologic test. When the chancre is single and appears in an area where it can be visualized, it is highly suggestive of syphilis, especially if a good history of venereal contact is elicited; dark-field examination of the lesion must nevertheless be carried out in every instance. The chancre may not be detectable; this is the case when it develops in the urethra. Dark field study may be of great help in making the diagnosis in the secondary stage of the disease; the "mucous patches" in the mouth or the perianal condylomata are a very good source of treponemes. If the dark field examination is positive and the serologic test negative, the serum should be restudied weekly for the first 2 to 3 weeks, and every few weeks thereafter.

The most important diagnostic procedure in syphilis is

serologic study. A number of variations of complement fixation and flocculation tests have been devised; certain ones are preferred over others by some laboratories. In our experience the Kahn and Hinton tests have proved very accurate. While these tests may be negative very early in the infection, seropositivity develops within a few weeks. They are positive in secondary and latent lues. In cases with neurologic involvement the reaction may also be obtained with the spinal fluid. Ten to 15 per cent of patients with cardiovascular syphilis have a negative Hinton reaction. While the blood and spinal fluid are positive in early tabes, they are negative in 25 per cent of cases in which tabes dorsalis has been present for some time. It is important to titrate the level of reagin in the blood in every case. This is of help in detecting biologic false positive reactions and in following response to therapy.

The serologic test for syphilis may be positive in some instances when the disease is not present; this is known as a biologic false positive reaction (BFP) and may be detected for only a short time (less than 3 months) or persist indefinitely. Acute BFP has been observed after cowpox vaccination and in malaria, infectious mononucleosis, and some cases of "viral" pneumonia. More or less permanent BFP is observed in some healthy individuals or in those in whom a chronic constitutional disorder such as disseminated lupus erythematosus, sarcoidosis, hemochromatosis, gout, or diabetes mellitus is present. The diagnosis of a biologic false positive reaction must not be made when the spinal fluid is abnormal and gives a positive serologic test.

A very helpful procedure in establishing the presence of, or ruling out, BFP is the treponema immobilization test (TPI). This reaction is never positive unless syphilis or some related spirochetal infection such as yaws is present; it usually appears at the same time as Hinton or Kahn positivity. It depends on the presence of antibody in the serum of luetic patients which, when mixed with spirochetes,

causes cessation of movement of the organisms. TPI is always negative in acute BFP reactions. It is positive in 98 per cent of untreated cases of late clinical or late latent syphilis. Sixty per cent of treated patients develop a negative TPI within 6 months; a negative test without therapy is extremely rare. Failure of the reaction to disappear after antiluetic treatment does not indicate a poor prognosis. Approximately 45 per cent of treated individuals with a persistently positive Hinton or Kahn reaction have a negative TPI. The treponema immobilization test is not a satisfactory procedure for evaluating the result of treatment; its persistence may be related to immunity to reinfection if the number of spirochetes to which a patient is exposed is small. In a rare case, TPI is positive in some instances when the usual serologic tests are negative, this indicates the presence of syphilis and has recently been described in some cases of cardiovascular lues.

The therapy of syphilis has been markedly simplified by the availability of penicillin. Metallotherapy need not be applied in any case. The treatment of early and late syphilis is the same, it is altered only when evidence of nervous system involvement is present. In patients with normal spinal fluid, the usual regimen consists of the intramuscular injection of 600,000 units of procaine penicillin daily for 10 days. When the spinal fluid is abnormal, the same type and quantity of antibiotic are employed for 15 days. It is not necessary to give bismuth prior to penicillin in cases of cardiovascular lues. The use of fever in paresis or taboparesis is no longer indicated. It should be pointed out that, regardless of how effectively penicillin eradicates the spirochetes from the tissues, it merely halts the disease at the point at which therapy is started Dysfunction of various organs already established will not be reversed; only progression will be arrested. *Some patients given penicillin develop fever and a variety of diffuse rashes within 6 to 12* hours after the first injection; this is the Jarisch-Herxheimer

reaction and does not contraindicate the further use of the antibiotic.

The ease with which syphilis can now be treated has made many physicians and patients complacent about this disease. Indeed, it has recently ceased to be the practice in some hospitals to carry out routine serologic testing in all patients admitted. The neglect of this procedure is to be decried, since it can result only in failure to detect and treat a significant number of cases. There has also been some relaxation in follow-up study of all contacts of a proved case of syphilis. This must always be carried out intensively in every instance. Syphilis has not yet been brought under control. While there was an appreciable drop in its incidence for some years after penicillin therapy became available, most recent surveys indicate that it is again increasing, especially in adolescents and young adults. This reflects some degree of neglect in detection of contacts and their treatment. The importance of this aspect of the problem of syphilis cannot be overemphasized. Unless it is intensively pursued, efforts at the control of this disease will fall short of their ideal goal.

Chancroid

The causative organism of chancroid is *Hemophilus ducreyi*. The average incubation period is 3 to 5 days, although it may be as long as 10 days or as short as 24 hours. There is a predilection for involvement of the skin rather than the mucous membranes. The common sites for development of lesions are the internal surface of the prepuce, frenulum, shaft of the penis, perineum, anus, scrotum, labia minora, clitoris, fourchette, vestibule, or cervix. In most cases the lesions are multiple and are present also on the lower abdomen and the thighs because of extension and autoinoculation. Far less commonly, the disease may in-

volve the hands, fingers, lips, and tongue. Extragenital lesions are more frequently seen in women than in men.

Four types of ulcers may occur. The most benign of these is transient and heals in 4 to 6 days. The second variety is a papular lesion which has characteristics of both chancroid and syphilis, which is often an associated disease. The third type is the so-called phagedenic ulcer in which there is rapid, progressive tissue destruction. The fourth is the giant ulcer which slowly increases in size until all of the skin of the thigh and scrotum is involved, becomes gangrenous, and is sloughed off.

The localized ulcerations which characterize chancroid are rarely accompanied by constitutional symptoms until the development of buboes. Fever, malaise, local pain, and leucocytosis occur in proportion to the degree of lymphadenitis, tissue destruction, and secondary infection. Pain is the most frequent symptom. Tenderness may be present at the site of the ulceration, but it usually accompanies the appearance of buboes and the development of lymphangitis. The inguinal glands may be so tender that walking is difficult. Phimosis and the development of a preputial lesion may make urination extremely uncomfortable.

In untreated cases the disease is characterized by the development of ulcers which last an average of thirty days, even when there is no contiguous spread. Some heal in a week, but others persist for as long as 3 months. The clinical course is variable and depends on the number of ulcers and the development of buboes which appear in half the cases and are most common (50 per cent) in the inguinal region. The ulcer begins as a painless macule at the site of inoculation and over a period of hours develops into a vesicle which pustulates and breaks down. When this occurs, there remains a sharply circumscribed shallow lesion, oval or circinoid in outline, with sharply defined, indurated, red edges. Secondary bacterial invasion occurs within a

short time. The clean base becomes shaggy and necrotic, and the sharp outline is lost as the ulcer enlarges and tends to merge with adjacent ones which have been formed either during the first infection or by autoinoculation. To be differentiated are the lesions of syphilis, lymphogranuloma venereum, and granuloma inguinale.

Lymphadenitis develops 3 to 4 days after the appearance of the ulcer. It is preceded by lymphangitis which presents as tender cords radiating from the skin lesion to the regional lymph nodes. When suppuration takes place, rupture often occurs, with the release of foul blood-tinged pus. Although healing may follow emptying of the bubo, the infected node sometimes closes before healing has started and the whole cycle is repeated.

The complications of chancroid are due to the disease itself or to the coexistence of another infection such as unrecognized syphilis or lymphogranuloma venereum. Fusospirochetal organisms may invade the chancroidal lesions and produce rapidly advancing and undermining ulceration. Balanitis, phimosis, paraphimosis, and destructive balanoposthitis may occur. Gangrene, with loss of large amounts of tissue on the medial aspects of the thighs, develops in some cases and spreads to involve the scrotum and penis which may be sloughed off.

The diagnosis of chancroid is frequently made clinically on the basis of the appearance of the lesions and the course of the disease. The causative organism is often difficult to isolate from the lesions. The presence of this infection is strongly suggested by gram-stained smears which reveal the characteristic gram-negative rods. Isolation of *H. ducreyi* in cultures made from bubo pus collected aseptically establishes the presence of the disease. The Ito-Riesteerna test (endermal injection of sterile bubo pus) is positive in 96 per cent of cases. A positive reaction indicates infection of longer than a weeks duration. Falsely positive tests

are observed in 10 per cent of patients most of whom have lymphogranuloma venereum. This disease and syphilis must always be ruled out.

Chancroidal ulcers, when untreated, heal very slowly. Local therapy is without benefit. Antimicrobial agents should be given as soon as the diagnosis is made. Sulfadiazine (full doses) cures most cases within 2 weeks with a low incidence of relapse. The tetracycline compounds (Aureomycin, Terramycin, Achromycin) are the drugs of choice. A dose of 0.25 to 0.5 gm. 4 times a day for 10 to 12 days heals the lesions in most instances within one week; the enlarged lymph nodes disappear rapidly. Antibiotics alone will not always cure the bubo; aspiration may be necessary. Incision and drainage are not advisable.

Granuloma Inguinale

The nature of the etiologic agent of granuloma inguinale has long been in doubt. However, at present it is thought by most observers that the characteristic Donovan body is a bacterium which can be cultivated by special technics. It has not been possible to transmit the disease using pure cultures of this organism, which is encapsulated, gram-negative, and shaped like a "closed safety pin". *Donovania granulomatis* does not grow on ordinary media, but will proliferate in the yolk sac of the embryonated chicken egg, in yolk-agar mixtures, and in Levinthal-beef heart infusion media. No laboratory animal is susceptible to infection

The lesions of granuloma inguinale are located on the external genitalia, perineum, and perianal region most frequently In the female, the vagina, cervix, body of the uterus, tubes and ovaries may be infected. About 5 per cent of cases have extragenital involvement. No area of the skin is immune. The scalp, eyelids, face, neck, trunk, extremities, lips, gums, mouth, pharynx, larynx, and colon may

short time. The clean base becomes shaggy and necrotic, and the sharp outline is lost as the ulcer enlarges and tends to merge with adjacent ones which have been formed either during the first infection or by autoinoculation. To be differentiated are the lesions of syphilis, lymphogranuloma venereum, and granuloma inguinale.

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A diagnosis of granuloma inguinale based on clinical features alone is never more than presumptive and is in error in about 30 per cent of cases. Many patients have a coexisting venereal disease. Although syphilis is most common, chancroid, lymphogranuloma venereum, and gonorrhea are not infrequent. These as well as secondary bacterial infection may so alter the appearance of the lesions as to make clinical diagnosis difficult or impossible. The presence of the disease is established by the demonstration of Donovan bodies in material obtained from the local lesions. Wright stained smears prepared from the friable and beefy-red area of the ulcer or from exudate aspirated from a pseudobubo are most helpful in diagnosis. Biopsy with tissue examination offers no advantage and is less reliable than a properly made smear.

One of the cardinal principles in the management of patients with granuloma inguinale is the recognition and therapy of coexisting venereal disease and secondary infections. Patients are best treated in the hospital. Although therapy need not be continued until the lesions are fully healed, it is important to recognize that relapses may occur as long as one year later. Streptomycin, Aureomycin, chloramphenicol and Terramycin are effective agents. Streptomycin and chloramphenicol cure the disease most rapidly. The former drug is given in a dose of 250 mg. every 6 hours intramuscularly; the latter is administered in the same quantity orally. Treatment should be continued for 10 to 12 days. Relapse occurs in some cases with all of the drugs, and requires retreatment About 5 per cent of cases are streptomycin-resistant.

Lymphogranuloma Venereum

The incubation period of lymphogranuloma venereum is 2 to 30 days. The initial lesion is a small, evanescent ulcer which appears on the external genitalia at the site of inocu-

be affected. Rarely, hematogenous dissemination produces widespread metastases in various organs, notably the bones and joints.

The individual lesion begins as a papule which slowly enlarges to produce a nodule from 1 to 4 cm. in diameter. An abscess may form and the fluctuant swelling may be mistaken for a suppurating lymph node; this is the "pseudobubo." Rarely the nodule may regress, but ulceration usually takes place. The margins of the ulcer are distinct and heaped up; the base is red, friable and spongy and covered with serosanguinous fluid. Spread occurs both by continuity and contact. Uncommonly, an exaggerated proliferative reaction may result in the growth of large vegetating masses which protrude from the base of the ulcer. Keloid-like lesions may appear. Secondary infection usually takes place and may produce a foul-smelling, shaggy, necrotic sore. With healing, atrophic depigmented scars develop and permanent loss of hair occurs.

Spontaneous healing is rare. Most untreated cases are slowly progressive. The odor resulting from secondary bacterial invasion and necrosis makes it increasingly difficult for patients to lead a normal social existence, and the appearance of the ulcers often makes them a source of horror. After many years, almost complete destruction of the external genitalia may occur, secondary infection becomes a problem, and death follows some intercurrent disease. The development of carcinoma at the site of long-standing lesions is surprisingly common.

The symptoms of granuloma inguinale are mostly attributable to the local lesions There is usually slight discomfort and profuse discharge. About a quarter of the patients have severe pruritus, while a smaller number suffer burning pain. Urinary complaints are common and usually are due to secondary bacterial infection. About 25 per cent of cases have a systemic reaction with fever, weight loss, and asthenia.

loma venereum and should be given in full doses for 2 weeks. The tetracycline compounds are also curative; the dose of these drugs is 0.5 gm. orally every 6 hours for 2 weeks. It should be stressed that none of the antimicrobial agents affects the late stages of the disease in which rectal stricture or elephantiasis are present. Buboes which have become fluctuant early in the course of the infection should be aspirated to prevent spontaneous rupture and subsequent sinus formation.

Tuberculosis of the Genital Organs

Tuberculosis of the prostate is usually associated with the same disease in the epididymis and seminal vesicles. Primary or isolated prostatic involvement is extremely rare. Renal tuberculosis is present in 25 per cent of cases.

The symptoms of tuberculosis of the prostate are the same as when other organisms invade the gland. The urine is turbid and contains tubercle bacilli. Terminal hematuria and bloody ejaculations may occur. The diagnosis is established by isolation and identification of the organism from the urine, from the prostatic fluid, or from tissue obtained by biopsy. Treatment is essentially the same as for pulmonary tuberculosis (Chapter VII).

Although any area of the female genital tract may be the site of tuberculosis, the Fallopian tubes are invariably involved and constitute the initial site of infection in the majority of cases. The occasional exceptions are those which follow intercourse with a male who has tuberculous epididymitis. Involvement of the pelvic organs and tuberculous peritonitis are, therefore, almost always secondary to primary disease of the tubes. Pulmonary tuberculosis is practically always present, the lesion in the lung frequently being inactive. Urinary and genital tuberculosis in the female are not commonly associated.

Tuberculosis is the cause of approximately 5 per cent of

lation and is seldom detected. The manifestations which usually attract the attention of the patient first are fever, malaise, and headache. Within a short time, the inguinal or femoral lymph nodes become enlarged forming the typical buboes which are usually bilateral, develop slowly, and form ill-defined lobulated masses. These lesions suppurate and may rupture, producing one or more draining fistulas. With bubo formation, headache, malaise, fever, and anorexia are prominent. These symptoms and lymphadenitis may subside spontaneously. Meningoencephalitis, keratitis, cutaneous lesions, and arthritis complicate the course of the disease in some cases.

Rectal involvement occurs many years after the acute stage of lymphogranuloma venereum. It is most common in females because the lymphatic drainage from the posterior portion of the vulva and vagina is to the perirectal and retroperitoneal lymph nodes. In the male, it is due to direct infection of the anorectal area because the lymphatic drainage from the penis is to the inguinal and deep iliac nodes. Proctitis develops with rectal bleeding and a purulent discharge. Eventually, scar formation takes place and may produce a complete fibrous ring leading to rectal stricture which may necessitate colostomy. Another late complication is elephantiasis of the external genitalia resulting from chronic lymphatic obstruction, ulceration and secondary infection of the chronically edematous tissues is common.

The diagnosis of lymphogranuloma venereum may be suspected on clinical grounds but can be proved by examination of tissue obtained at biopsy. The Frei test (best carried out with Lygranum) is positive but does not indicate the stage of the disease because it remains positive for many years after the acute phase of infection. Complement-fixation studies are helpful; a rising titer as demonstrated by study of serum specimens obtained at least 2 to 3 weeks apart is diagnostic.

Sulfadiazine is effective in the [illegible] of lymphogranu-

that this type of chronic salpingitis and endometritis cannot be completely cured in some cases by tuberculostatic agents alone and recommend salpingectomy and hysterectomy. Both tubes usually have to be removed because involvement is practically always bilateral. The ovaries often can be spared since only the tunica is usually involved, and chemotherapy alone may be curative. Patients who have undergone medical therapy should be studied carefully and frequently after completion of treatment, since relapse of the disease is not rare; recrudescence indicates the necessity for surgical treatment.

ll cases of salpingitis. With the ease of treatment of gono-
occal infection, there is reason to believe that the percent-
ge of chronic tubal disease due to the tubercle bacillus will
radually increase.

Tuberculous endometritis, a frequent cause of sterility,
always secondary to tubal involvement but occurs in less
an 50 per cent of patients with salpingitis. Infection of
e tubes may be present, however, without endometritis.
lberculous oophoritis never occurs in the absence of dis-
se of the tubes and tends to heal spontaneously after re-
oval of the infected salpinx. Vaginitis and vulvitis are
tremely rare and probably related to infection higher in
e genital tract, they are characterized by the presence of
ulcerative lesion which may resemble a luetic chancre
even a carcinoma.

There are no characteristic clinical features of tuberculous
pingitis. The manifestations are identical with those pres-
: with other types of chronic tubal infection. The diag-
sis of this disease is rarely made clinically. The following
lings may suggest its presence: (1) the demonstration of
erculosis of the lungs, bone, or disseminated disease, and
the presence of adnexal inflammatory masses in virgins
vomen in whom the possibility of gonorrhea can be com-
tely ruled out. The symptoms may be exaggerated at the
e of menstruation. The clinical picture of tuberculous
ometritis is not always typical There may be a per-
ent, watery, or slightly bloody discharge. Oligomenor-
a and amenorrhea are frequent. As a rule, however, the
ifestations of the tubal involvement bring the patient to
physician The diagnosis of tuberculous endometritis is
le by curettage which reveals the characteristic lesions;
ure may yield the tubercle bacillus.

oth medical and surgical treatment of tuberculosis of
internal female genitalia may be required. Chemother-
is the same as for tuberculous infection of the lungs
apter VII). Many gynecologists are of the opinion

fontanelles in young infants is more suggestive of meningitis but again does not prove the existence of this disease.

Signs of meningeal irritation (stiff neck and back, and positive Kernig and Brudzinski signs) are present when the meninges are inflamed and are usually demonstrable in cases of bacterial meningitis. However, it must be stressed that these findings are not invariably present even with bacterial disease of the meninges, and that, conversely, they may be detected in the total absence of meningeal disease. In infants under 6 months of age it is very unusual to find any signs of meningeal irritation in the face of severe bacterial meningitis; the most important sign in this age group is bulging of the fontanelles. Some young children, particularly those with upper respiratory tract infections or with right upper lobe pneumonia, may have a very stiff neck and back and a positive Kernig's sign with completely normal spinal fluid, this is known as meningismus. Localized disease in the neck or back may also be very misleading.

The presence of meningitis can be established only by examination of spinal fluid. In most cases, the intraspinal pressure is elevated. There is an increase in the number of cells, but this is very variable; the total number may range from 20 to more than 100,000 per mm^3. The writer has seen patients with meningococcal and pneumococcal meningitis in whom the spinal fluid contained many organisms but not an abnormal number of cells. Neutrophiles usually constitute 95 per cent of the cells present. The sugar content is decreased and may be zero, a simultaneous determination of blood sugar should always be carried out. In diabetics with hyperglycemia, a spinal fluid sugar of 100 mg. per 100 ml. must be considered low for example if, at the same time, the blood sugar level is 500 mg. per 100 ml. The protein content of the spinal fluid is elevated to a varying degree, it may be so high as to cause the fluid to clot spontaneously. Determination of chloride is of little or no diag-

CHAPTER XIII

INFECTIONS OF THE NERVOUS SYSTEM

Bacterial Meningitis—General Features

Bacteria are the commonest cause of meningitis, although viruses are responsible for some cases. The meningococcus, influenza bacillus, pneumococcus, and tubercle bacillus are the organisms most often involved but a number of other species may also produce the disease. The writer has studied patients with meningeal infections due to *E. coli, Salmonella*, beta, alpha, and non-hemolytic streptococci, staphylococci, *B. anthracis, Ps. pyocyaneus, Proteus, Alcaligenes fecalis, B. subtilis*, and the Friedlander bacillus. Most bacterial meningitides cannot be differentiated clinically. Isolation and identification of the causative agent is the only method of establishing the specific etiology.

The signs and symptoms of bacterial meningitis are mainly non-specific and, with occasional exception, do not point to the organism involved. All patients have the general manifestations of infection—fever, chills, malaise, generalized aching, varying degree of prostration, and leucocytosis. If, in addition to these, stupor, coma, convulsions, delirium, localizing neurologic findings, or cranial nerve palsies are present, attention is directed more actively toward the possibility of meningeal infection, although even these manifestations may occur in the absence of nervous system involvement. The presence of severe headache, vomiting, engorgement of retinal veins, papilledema, or bulging

fontanelles in young infants is more suggestive of meningitis but again does not prove the existence of this disease.

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nostic value, since it merely reflects the plasma chloride level which is often depressed by fever and vomiting. As recovery from bacterial meningitis occurs, usually under the impact of antibiotic therapy, characteristic changes are observed in the spinal fluid. The total cell count decreases and, simultaneously, the percentage of lymphocytes increases rapidly. The sugar rises to normal levels, while the protein content is reduced. It is during this period of recovery that the findings may be misinterpreted as indicating an "aseptic" meningitis, if the physician is not aware of the precise nature of the infection.

The specific etiologic diagnosis of bacterial meningitis depends completely on identification of the organism. The first procedure to be carried out is a gram stain of the sediment of centrifuged spinal fluid. The morphology of the organism and its reaction with the gram stain often indicate the genus to which it belongs. The demonstration of capsular swelling is specifically diagnostic; this is possible with *H. influenzae, K. pneumoniae,* the meningococcus, and pneumococcus. When these bacteria are involved, it may be possible to detect their presence even when smears do not reveal them. Layering a small amount of specific antiserum over the spinal fluid in a capillary tube results in formation of a precipitate at the interface if capsular polysaccharide is present. The petechiae in meningococcal meningitis may contain gram-negative diplococci which are readily demonstrable in gram-stained smears made from material obtained from the central area of the lesions in some cases.

All spinal fluids should be cultured whether or not organisms are observed in direct smear. It is best to incubate all cultures in an atmosphere of 10 per cent carbon dioxide and to discard them only if they still show no growth after 7 to 10 days. In addition to the "routine" media, Saboraud's or corn meal agar and thioglycollate broth should be inoculated to rule out the presence of yeasts, fungi, and anaerobic bac-

teria in cases in which organisms cannot be recovered by the usual procedures. Attempts should also be made to isolate tubercle bacilli.

The age of the patient, the presence of predisposing factors, the preceding illness, and the onset and course of a bacterial meningitis are very helpful in directing the attention of the physician to the specific etiologic agent in some instances. For example, the commonest causes of meningeal infection in children under 6 months of age are *E. coli* and *Salmonella*. *H. influenzae* produces infection most often in patients 6 months to 3 years old; the disease is very rare in adults except after operations or injuries to the skull and brain, after lumbar puncture, or when, as a result of congenital defects or injury, there is a connection between the subarachnoid space and the upper respiratory passages. When meningitis follows lobar pneumonia in adults, it is usually produced by the pneumococcus Meningeal infections appearing after a sore throat or bronchopneumonia in young children are often caused by *H influenzae*. Involvement of the meninges secondary to purulent otitis media or sinusitis is most frequently due to *Staph. aureus*, the pneumococcus, or beta-hemolytic streptococcus. In patients with more than one episode of bacterial meningitis, the organisms most likely to be involved are first the pneumococcus, and second *H. influenzae*. Some of these individuals have a history of head injury, may have had episodes of spinal fluid rhinorrhea, and usually have dural tears. Friedlander bacillus meningitis is observed primarily in diabetics. *Ps. pyocyaneus* is often responsible for meningitis which develops after lumbar puncture. Contact with a known case of tuberculosis must always suggest the possibility of tuberculous meningitis. When a macular or petechial rash is present, the disease is practically always produced by the meningococcus.

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Involvement of the 6th and 7th nerves may be unilateral or bilateral and usually clears in 1 to 12 months. When the 8th nerve is damaged, however, permanent bilateral loss of hearing is the rule. The eye may be extensively involved; purulent conjunctivitis, retinal hemorrhages, optic neuritis, papilledema, and endophthalmitis with resultant permanent blindness have been observed. Acute ulcerative endocarditis may develop; the mitral valve, which may previously have been normal, is the one most often infected. Pericarditis with purulent or sterile pericardial effusion, diffuse myocarditis, and multiple myocardial abscesses containing meningococci have been noted. Severe pain in all of the large joints may be a prominent feature very early in the disease, there are usually no objective findings. At the height of the meningitis, a migrating polyarthritis may appear; the fluid in the joint spaces is purulent, contains organisms, and has a reduced quantity of sugar. During convalescence, several of the large joints may become swollen and painful; the fluid is sterile, although it is characterized by an increased number of cells, many of which are neutrophiles. Otitis media, epididymitis, orchitis, salpingitis, and diffuse meningococcal bronchopneumonia may also occur.

One of the most serious complications of meningococcal meningitis is bilateral adrenal hemorrhage, the so-called Waterhouse-Friderichsen syndrome. Clinically, this is characterized by hypotension, fever, the presence of numerous large hemorrhages in the skin, and stupor or coma Considerable confusion exists concerning this diagnosis during life. The mere fact that a patient has severe meningococcal infection and is in shock does not prove that acute adrenal insufficiency is present. In many of the cases which have been described as examples of this syndrome, the chemical evidence necessary to support the possibility of adrenal destruction is not available. Many clinicians are of the opinion that the Waterhouse-Friderichsen syndrome is a pathological entity only. The entire picture can be explained in

Meningococcal Meningitis

Meningococcal meningitis occurs at all ages in epidemics; sporadic cases are most frequent in patients less than 2 years and between 10 and 40 years old. The incubation period is 1 to 10 days. Three types of onset have been described: (1) Following a mild upper respiratory infection of 1 to 3 weeks duration, (2) after upper respiratory disease of only a few days duration, (3) sudden, explosive onset without symptoms of previous illness. The organisms reach the meninges by the hematogenous route; blood cultures are positive in 25 to 80 per cent of cases.

The signs and symptoms of this kind of meningitis are the same as are generally present in other types of bacterial infection of the meninges. The main feature which distinguishes meningococcal meningitis is the rash. The eruption frequently starts as pink, irregular, macular lesions which are morbilliform in character and are most numerous on the extremities. In most cases petechiae are also present; they are often detected on the conjunctivae and buccal mucous membranes. In severe infections, hemorrhages develop in the retinae and there may be large ecchymotic areas (suggillations) in the skin.

A large variety of complications may occur mainly in untreated cases. Many of these are due to metastatic foci of infection secondary to the bacteremia which is so common in the disease. Gangrene, loss of skin, and spontaneous amputation of digits and portions of the ear lobes may occur. Herpes simplex is present early in convalescence or in the acute phase in the majority of cases. Herpes zoster may also appear. Among the nervous system complications which have been described are permanent changes in mentality, manifestations of encephalitis, cerebral thrombosis, brain abscess, hemiparesis, hemiplegia, hemianopsia, aphasia, hydrocephalus, myelitis, and cranial nerve palsies. The cranial nerves affected most frequently are the sixth, seventh and eighth.

coccal meningitis who are in shock. The mechanism of the shock of infection is unknown, however; it does not appear to be related to acute adrenal insufficiency except in rare instances. Since there is both experimental and clinical experience to indicate that cortisone affects deleteriously various types of infections, one must use these potent drugs only with considerable reservation and with the most careful supervision of the patient. Support of the blood pressure with vasoconstricting agents such as norepinephrine and treatment of the infectious process with intensive chemotherapy are the most important and dependable maneuvers in eliminating the hypotension.

Cases of meningococcal meningitis treated with sulfonamide in the manner recommended above usually are afebrile within 48 hours. Stupor, coma, and confusion often clear more slowly, although normal sensorium usually returns in 3 to 4 days in most instances. The complications described above are seldom seen when antimicrobial agents are given. However, the writer has observed 8th nerve involvement, aseptic hydrarthrosis, sterile pericardial effusion, and spontaneous cerebral venous thrombosis in patients responding satisfactorily to therapy. The fatality rate has been remarkably reduced by treatment. It is very uncommon today for patients to succumb to meningococcal meningitis, unless it is explosive in onset and overwhelming in its course; in such individuals the entire duration of the infection from the time of appearance of the first symptom to death may be no longer than 12 to 18 hours.

H. Influenzae Meningitis

H. influenzae is the commonest bacterial cause of meningitis in children between the ages of 6 months and 3 years. It is very uncommon in adults. About three-fourths of babies have a preceding upper respiratory infection and about one-half a bronchopneumonia due to the influenza bacillus.

most cases on the basis of overwhelming infection alone. The writer has observed patients with meningococcal meningitis who, during life, exhibited all of the features said to be pathognomonic of this syndrome but who, at necropsy, showed no evidence of adrenal damage.

The diagnosis of meningococcal meningitis is suspected clinically when the general manifestations of infection, signs of meningeal irritation, and a macular or petechial rash are present. It is proved by demonstrating the typical biscuit-shaped gram-negative diplococci in the purulent spinal fluid which has a reduced sugar content. Petechial smears, stained by the Gram method, are helpful in some instances in revealing the organisms. Blood culture may yield the bacteriologic diagnosis before the bacteria can be cultured from the spinal fluid.

The agent of choice in the treatment of meningococcal meningitis is a sulfonamide. Both sulfadiazine and sulfisoxazole (Gantrisin) have been employed with success. The initial treatment should be given parenterally. In adults, 5 gms. of the sulfonamide (sodium salt) is given intravenously, *after* adequate hydration has been accomplished. One gm. of the same drug is then administered subcutaneously every 4 hours for the first day or until the patient is able to swallow safely. Thereafter, one gm. of the drug is administered orally every 4 hours for one week. Blood level determinations should be carried out at least every other day, and the sulfonamide concentration maintained between 8 and 12 mg. per 100 ml. It has been suggested that patients who appear to have fulminating, overwhelming infection when first seen should be given aqueous penicillin (500,000 units intramuscularly every 3 hours) in addition to the sulfonamide.

Treatment of what clinically appears to be the Waterhouse-Friderichsen syndrome by the use of cortisone or other corticosteroids is still an unsettled matter. Some physicians always administer these drugs to patients with meningo-

cin is given; the dose for children under 1 year of age is 15 mg., for those between 1 and 3 years 25 mg., and for older patients 35 mg. The drug is dissolved in 10 ml. of saline and injected intrathecally in the lumbar area over a period of 10 minutes. Approximately 15 ml. of spinal fluid should be removed before the antibiotic is injected. In addition, 0.5 to 1 gm. per day of streptomycin is given intramuscularly (divided into 4 injections per day) and a sulfonamide (in the doses recommended) is administered. Only *one* intrathecal treatment is necessary, the remainder of the therapy is continued for 2 weeks. The writer has never observed a reaction to intrathecally-administered streptomycin; the most important points in averting difficulty are (1) never exceeding the recommended dose, (2) adequate dilution, and (3) slow injection of the drug.

Pneumococcal Meningitis

Pneumococcal meningitis occurs in about 50 per cent of cases without a discoverable primary focus. In the other half, *it follows infection of the middle ear, paranasal sinuses,* and lung most often, although it has also been described after purulent conjunctivitis and acute pneumococcal cholecystitis. The disease is seen occasionally in patients who, as a result of previous trauma or some congenital defect, have a tear in the dura with a connection between the subarachnoid space and the upper respiratory structures; these people may have spinal fluid rhinorrhea and are subject to repeated attacks of pneumococcal meningitis. This type of meningeal infection appears most frequently at two age levels: in young children in whom suppurative otitis media is common, and in adults over the age of 40 in whom pneumococcal (lobar) pneumonia is relatively frequent.

The clinical features of pneumococcal *meningitis do not* suggest its etiology in the "primary" cases. It must be *seriously* considered, however, in all instances in which one of

There are no specific diagnostic clinical findings other than the signs of meningeal irritation and the abnormal spinal fluid. Convulsions are quite common. Skin eruptions do not occur. The incubation period is 1 to 7 days. Ninety-five per cent of cases are produced by type b organisms. Bacteremia is present in from 25 to 50 per cent.

The complications of influenzal meningitis may be the same as those observed with meningococcal infection. The most common ones are hydrocephalus due to obstruction of the aqueduct of Sylvius by exudate, subdural empyema, cerebral vein thrombosis which may be very extensive and produce complete cortical necrosis, and subdural collections of sterile fluid. The last two occur even in treated cases; sterile subdural fluid is said to be present in 50 per cent of cases which respond effectively to antimicrobial agents.

The diagnosis of influenzal meningitis is established by demonstration of the typical gram-negative, pleomorphic rods in stained smears and by culture of the spinal fluid. The identity of the organism is confirmed by the capsular swelling test. With this procedure, the etiology is absolutely established within one hour after admission to the hospital in many cases.

Two methods of treatment are successful in *H. influenzae* meningitis. Therapy must be instituted *immediately* after the diagnosis is suspected because any delay until results of bacteriologic culture become available worsens the outlook for recovery. The death rate in untreated influenzal meningitis approximates 100 per cent. Patients may be treated with chloramphenicol (75 mg. per Kg. in divided doses per day) plus sulfadiazine or sulfisoxazole (0.1 gm. per pound per day, the initial dose being one-half of the daily required quantity); it is preferable to give both drugs parenterally for at least 24 hours and to continue therapy orally, after consciousness returns, for 2 weeks. The writer prefers the following regimen of treatment: Immediately after the diagnosis is made, a *single* intrathecal injection of streptomy-

cin is given; the dose for children under 1 year of age is 15 mg, for those between 1 and 3 years 25 mg, and for older patients 35 mg. The drug is dissolved in 10 ml. of saline and injected intrathecally in the lumbar area over a period of 10 minutes. Approximately 15 ml. of spinal fluid should be removed before the antibiotic is injected. In addition, 0.5 to 1 gm. per day of streptomycin is given intramuscularly (divided into 4 injections per day) and a sulfonamide (in the doses recommended) is administered. Only *one* intrathecal treatment is necessary; the remainder of the therapy is continued for 2 weeks. The writer has never observed a reaction to intrathecally-administered streptomycin; the most important points in averting difficulty are (1) never exceeding the recommended dose, (2) adequate dilution, and (3) slow injection of the drug.

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The clinical features of pneumococcal meningitis do not suggest its etiology in the "primary" cases. It must be seriously considered, however, in all instances in which one of

the predisposing lesions described above is present. The diagnosis is confirmed by demonstration of the typical lanceolate, encapsulated gram-positive diplococci in smears and cultures of the spinal fluid, and establishing their identity by capsular swelling with type-specific serums.

The fatality rate in untreated pneumococcal meningitis approximates 100 per cent. Among the complications which have been observed are acute endocarditis, brain abscess, cortical thrombophlebitis with necrosis, subdural empyema, cranial nerve palsies, and hydrocephalus.

The availability of potent antimicrobial agents has greatly improved the outlook for survival in pneumococcal meningitis, but recovery does not occur in all cases. Certain features of the disease are important in the prognosis in the treated patient. (a) *Age:* The risk of death is greatest in individuals younger than 2 and older than 50 years of age. (b) *The mode of onset:* The outlook is best if there is no discoverable focus from which the meningeal infection arose, worst when it follows pneumococcal pneumonia, and intermediate when it is secondary to disease of the ears or paranasal sinuses. (c) *The serologic type of pneumococcus:* Types 3 and 8 are associated with the highest mortality. (d) *Bacteremia:* A positive blood culture worsens the prognosis. (e) *The presence of complicating disease or debilitating disorders.* (f) *Delay in initiation of treatment.*

There are two methods for the treatment of pneumococcal meningitis. *Method I:* Aqueous penicillin G, in a dose of 1 million units, is injected intramuscularly every 2 hours for 2 weeks; this is the procedure preferred by most clinicians. The writer feels, however, that this regimen does not offer the best possibility of cure and has been using the following therapeutic approach for a number of years. *Method II:* In adults, 30,000 units of crystalline benzyl penicillin G is injected intrathecally in the lumbar area immediately after the diagnosis is made. The injection is repeated 12 and 24 hours later; no more than 3 doses are given. The intrathecal

dose is reduced to 3000 to 5000 units for babies and 10,000 units for older children. The penicillin must be dissolved in 10 ml. of physiologic salt solution and, after 15 ml. of spinal fluid have been removed, injected into the spinal space over a 10 minute period. In addition, 100,000 units of the same kind of penicillin is given intramuscularly every 4 hours, and sulfadiazine or sulfisoxabole is administered, in *the usual quantities, parenterally for the first 24 to 48 hours* and orally thereafter. Therapy is continued for 2 weeks. No reactions to intrathecally-injected penicillin G have been observed when dosage, concentration, and speed of injection have been rigidly controlled.

Tuberculous Meningitis

Tuberculous meningitis is primarily a disease of young children, although it may occur even in elderly patients. About 50 per cent of the cases are 2 years of age or younger; 25 per cent are 2 to 4 years old. Approximately 40 per cent have negative tuberculin reactions at the time the disease starts.

Five mechanisms are responsible for the clinical picture of tuberculous meningitis. (1) tuberculin sensitivity, (2) vascular obstruction with arteritis and phlebitis leading to thrombosis and localizing brain or spinal cord signs, (3) extension of the infection from the meninges to the cerebral cortex producing the picture of encephalitis, (4) mechanical irritation due to the exudate which is present in largest quantities at the base of the brain, and (5) interference with outflow of cerebrospinal fluid by exudate causing the development of internal or external hydrocephalus.

The early clinical course of tuberculous meningitis is often not suggestive of meningeal infection. Fever, anorexia, insomnia, loss of weight and marked hyperirritability may be present for 2 to 3 weeks before headache, signs of meningeal irritation, and other manifestations of acute meningitis

appear. Once the meningeal infection is apparent clinically, there is very little even then that makes the physician suspicious of tuberculosis. Convulsions are relatively common and stupor and coma are frequent. The development of certain localizing signs and the character of the spinal fluid may allow a presumptive diagnosis, however. Very suggestive is the sudden appearance of hemiplegia in a young child or the development of bilateral 6th cranial nerve palsy.

If the spinal fluid is studied very early in the course of the disease, it usually reveals 200 to 500 cells per mm^3 (more than half of which are polymorphonuclear leucocytes), a moderately increased protein, and a normal sugar content (compared to the blood sugar). Within a few days, however, the bulk of the cells are lymphocytes and the sugar begins to be reduced in quantity. Examination of acid fast stained smears of spinal fluid rarely reveals tubercle bacilli. The tentative diagnosis of tuberculous meningitis can be made on the basis of a spinal fluid in which lymphocytes are predominant, in which a fall in sugar content is detected by serial study (every other day), and from which no organisms can be cultured using ordinary media, Saboraud's agar and thioglycollate broth.

There is a form of meningeal reaction in tuberculosis which is not due to bacterial invasion but which may resemble true meningitis in some respects; this is the "serous" meningitis of tuberculosis. It results from stimulation of a latent tuberculous meningeal focus by activation of a pulmonary lesion; this produces a sterile inflammatory reaction in the meninges with spinal fluid changes which are the same as those present in true tuberculous infection, except for the fact that the sugar level always remains normal and *M. tuberculosis* cannot be isolated. "Serous" meningitis usually subsides spontaneously and requires no special treatment other than that indicated for the management of the pulmonary lesion.

The specific diagnosis of tuberculous meningitis is es-

tablished by isolation of tubercle bacilli from the spinal fluid in culture or by guinea pig inoculation. It is unwise, however, to wait for bacteriologic confirmation of the clinical suspicion because *the average duration of life in the untreated disease is only 18 to 21 days*, whereas the cultures or animal studies may require 4 to 6 weeks before positive results are obtained. For this reason, it is necessary to institute therapy on the basis of the clinical features and the spinal fluid findings. A positive tuberculin reaction in a young child, in the presence of suggestive spinal fluid changes, is sufficient evidence on which to start treatment.

The best method for the treatment of tuberculous meningitis is the simultaneous administration of streptomycin, isonicotinic acid hydrazide (INH), and para-aminosalicylic acid (PAS). Streptomycin is injected daily in a dose of 0.5 to 1 gm, depending on the age and size of the patient. The oral dose of INH is 10 to 12 mg. per Kg. per day; 100 mg. of pyridoxine daily must be given simultaneously to prevent neurologic complications. Ten to 12 gms. of PAS are administered per day (divided into 4 doses) to adults; the quantity is reduced in children, according to their size. A glass of milk after each dose is helpful in reducing gastrointestinal irritation. There is considerable question concerning the necessity for the use of intrathecal streptomycin, since treatment with three antituberculous drugs has become the practice. Chemotherapy should be continued for a minimum of one year. ACTH and cortisone have been administered together with tuberculostatic agents for 1 to 2 months by some clinicians. Although it has been suggested that the disease ameliorates more quickly and the survival rate increases, this still remains to be proved. The possible deleterious effects of corticosteroids on infection must always be kept in mind The survival rate in tuberculous meningitis treated with streptomycin, isonicotinic acid hydrazide and para-aminosalicylic acid is 80 to 85 per cent. Certain factors are of importance in determining the outcome of therapy.

The following indicate a questionable or relatively poor prognosis: (1) age less than 3 years, (2) stupor or coma, especially with convulsions before initiation of treatment, (3) the presence of a pulmonary parenchymal lesion, (4) Negro race, (5) miliary tuberculosis, (6) delay in diagnosis and treatment, (7) *abnormal electroencephalogram*, and (8) disease caused by organisms resistant to the drugs. Spinal block or hydrocephalus may occur. A salt-losing syndrome is sometimes observed early, but disappears as the drugs exert their effect.

OTHER TYPES OF BACTERIAL MENINGITIS

Types of bacterial meningitis other than those described above are usually suspected only on the basis of the mode of onset, nature of the preceding illness, and the course of the disease. Their exact nature can only be detected by identification of the specific bacteria in the spinal fluid. Treatment for each depends on the sensitivity of the causative organism to various antibiotic agents. In most cases, it is best to continue therapy for at least 2 weeks. Chloramphenicol is the agent for the management of meningitis due to *E. coli* or *Salmonella* species, and should be given to babies in a dose of 75 mg. per Kg. per day divided into 4 equal quantities; the dose for adults is 0.5 gm every 6 hours. For staphylococcal meningitis, either 1 million units of penicillin given every 2 hours intramuscularly, or chloramphenicol plus erythromycin (0.5 gm. of each every 6 hours) may prove effective. Because of the increasing number of antibiotic-resistant strains of *Staphylococcus*, it is imperative that the responsible strain be examined promptly for sensitivity to such drugs as bacitracin, novobiocin, and neomycin. Polymyxin B (25 to 50 mg. intramuscularly every 6 hours) is probably the best agent for the management of *Ps. pyocyaneus* meningitis; some clinicians give 1 to 2 mg. of the drug

intrathecally daily for several days, in addition. In meningitis due to the Friedlander bacillus, the administration of streptomycin (1 gm. intramuscularly per day) plus chlormaphenicol (1 gm. every 6 hours) has been recommended.

Brain Abscess

Brain abscesses are usually secondary to infections of the cranial bones, middle ear, mastoid, paranasal sinuses, and lungs; they also may follow compound fractures of the skull, meningitis, and bacteremia with metastatic focalization. They may be located in the extradural, subdural or subarachnoid spaces, or within the brain substance. The nature of the organism which produces them is determined, in part, by the focus from which they arise; many are due to *Staph. aureus*. Extradural abscess is frequently a sequel to infection of the tip of the petrous process and is manifested by 6th nerve paralysis and pain in the temporal region (Gradenigo's syndrome). Subarachnoid lesions are uncommon and subdural ones rare. The most frequent site is within the brain itself, the area infected being related in some degree to the focus from which the disease originates. Abscesses which follow otitis media are usually situated in the temporal lobe or cerebellum, while those which are secondary to sinusitis are often present in the frontal lobes. Single lesions complicate paranasal sinusitis and pulmonary infections, especially bronchiectasis. Bacteremia usually results in diffuse seeding of the brain with the development of multiple abscesses.

The early manifestations of brain abscess are due to a cerebritis characterized pathologically by a diffuse and often severe inflammatory reaction. The symptoms may be very severe during this time. In the *second phase*, purulent exudate begins to form but localization of the lesion has not yet occurred. In the final stage, the abscess becomes encap-

sulated; general signs of infection may be minimal at this time, the most striking findings being those of an expanding intracranial lesion which may be mistaken for tumor.

Brain abscess should be considered in any patient who has had a predisposing infection and then develops fever plus manifestations of increasing intracranial pressure or localizing neurologic signs, or both. It is imperative that this disease be suspected early, because without proper therapy the fatality rate is as high as 90 per cent. Repeated study of the eyegrounds for papilledema is imperative. Detailed neurologic examination should be carried out at frequent intervals in a suspected case so that signs of localization may be detected at the earliest possible moment.

The cerebrospinal fluid may be entirely normal. If, however, the abscess lies close to the meninges or to the ventricles, a sterile inflammatory reaction may occur; when this happens the spinal fluid cells increase in number (mostly lymphocytes) and the protein content rises; the sugar level is normal. Spinal fluid pressure is frequently elevated, the height depending on the stage of the abscess and its location. Great care must be exercised in carrying out lumbar puncture in patients in whom there is a considerable degree of increased intracranial pressure because of the great risk of herniation of the medulla and sudden death. If only a few drops of fluid are obtained through a narrow gauge needle, however, no difficulty may arise and enough information may be derived to rule out a purulent meningitis.

Untreated brain abscesses may spread, lead to the production of diffuse thrombosis of the venous sinuses, or rupture into the ventricles or subarachnoid space causing herniation through the tentorium and rapid death.

The treatment of brain abscess combines both medical and surgical approaches. As soon as the possibility is suspected, patients should be given 1,000,000 units of aqueous penicillin every 2 to 3 hours intramuscularly and be seen immediately by a competent neurosurgeon. The best results

are obtained when, following a variable period of chemotherapy, the lesion is excised. Most cases which recover after such treatment have some neurologic residua, the nature depending on the portion of brain involved. Some clinicians are of the opinion that chemotherapy alone will produce cure in some instances; this may be so if the disease is diagnosed during the early stage of cerebritis and intensive antibiotic therapy instituted.

Spinal Epidural Abscess

Spinal epidural abscess may result from direct infection from adjacent lesions such as decubitus ulcers, wounds in the back, perinephric or psoas abscesses, or osteomyelitis of the spine. More commonly, it is a metastatic infection resulting from hematogenous dissemination of organisms by bacteremia associated with furunculosis of the skin, mastoiditis, periodontal abscesses, cystitis, cellulitis, and even upper respiratory tract infections.

Because many instances of epidural abscess are secondary to skin infections, the organism most often responsible is *Staph. aureus*. The pneumococcus, beta-hemolytic streptococcus, *Ps. pyocyaneus*, and *Brucella* are rarely the causative agents.

The first manifestations of spinal epidural abscess are those of infection (fever, chills, generalized aching, and leucocytosis). Very often a history of a preceding lesion, especially of the skin, within 2 to 4 weeks is elicited. The first localizing manifestation is pain in the back which develops within a month of the predisposing infection, appears suddenly, is aggravated by movement, and may be so severe that it is not relieved by opiates. Percussion over the spine reveals localized tenderness in the area of the abscess. The next phase of the disease develops in from 2 to 42 days (average 6 days) after the onset of pain and is characterized by progressive neurologic dysfunction. Flaccid paralysis,

complete anesthesia, arreflexia, and loss of sphincter control appear with great rapidity below the level of the lesion. Lumbar puncture usually reveals a varying degree of block. The spinal fluid may contain an increased number of lymphocytes; the protein content is always elevated, often to very high levels. Froin's syndrome (xanthochromic spinal fluid which clots on standing) may be present.

The possibility of spinal epidural abscess should be suspected in any patient with the general manifestations of infection who has pain and localized tenderness in the back and shows evidence of rapidly progressive sensory and motor loss.

The treatment of spinal epidural abscess is primarily surgical. The earlier the diagnosis is made and proper therapy carried out, the less the chance for residual neurologic deficits for, as a rule, the sensory and motor changes present at the time of laminectomy do not regress. Since most cases are due to staphylococcal infection, it is best to administer aqueous penicillin (500,000 to 1,000,000 units intramuscularly every 4 hours) prior to and for 2 to 3 weeks after operation. The problem of drug-resistant staphylococci may present itself. As soon as the bacteria are isolated from material obtained during drainage of the abscess, they should be studied for susceptibility to chloramphenicol, erythromycin, bacitracin, novobiocin, penicillin, and neomycin, and the antibiotic used to which they are most sensitive. In most cases which occur outside the hospital, the staphylococci are susceptible to penicillin.

NEUROSYPHILIS

Asymptomatic neurosyphilis is characterized by the presence of abnormal spinal fluid alone. Its detection is very important since it may be the precursor of symptomatic disease. The more marked the changes in the spinal fluid, the greater the possibility that neurologic dysfunction will appear later. Three types of spinal fluid changes may be

observed: *Grade I*—present in 8 per cent of cases; increased number of cells or quantity of protein, or both. *Grade III*—present in 21 per cent; increase in cells and protein, a strongly positive serologic reaction, and a first zone colloidal gold reaction. *Grade II*—present in 16 per cent of patients; changes intermediate between Grades I and III. Symptoms of nervous system disease may appear within 10 years of the time spinal fluid abnormalities are first detected. If the spinal fluid is negative 5 years after the onset of syphilis, it rarely becomes positive.

Syphilitic meningitis usually appears within two years after infection It may occur without obvious provocation or develop during the early course of treatment with metals, when it is referred to as a neurorelapse. Three syndromes may be present. (a) cranial nerve palsies and basilar signs, (b) symptoms referable to the vertex of the brain—convulsions, hemiplegia, delirium, and aphasia, and (c) increased intracranial pressure with nausea, vomiting, headache, papilledema, and signs of meningeal irritation.

Meningovascular syphilis is usually manifested by signs of thrombosis of one or more branches of the cerebral or spinal arteries producing monoplegia, hemiplegia, hemianesthesia, aphasia, or hemianopsia. Cranial nerve palsies are frequent, and convulsions may occur Involvement of the spinal cord produces a transverse myelitis with progressive paralyses and sensory disturbances. When the pyramidal tracts are affected, Erb's spastic spinal paraplegia develops. Degeneration of the anterior horn cells may take place and lead to the appearance of a neurologic picture difficult to distinguish from progressive muscular atrophy. Localized gummas of the spinal cord may resemble tumor.

Tabes dorsalis is due to selective syphilitic degeneration of the posterior roots of the spinal nerves and posterior columns of the spinal cord. Manifestations usually appear 20 to 30 years after infection and consist of "lightning" pain and paresthesias. Severe attacks of abdominal pain, nausea, and

complete anesthesia, arreflexia, and loss of sphincter control appear with great rapidity below the level of the lesion. Lumbar puncture usually reveals a varying degree of block. The spinal fluid may contain an increased number of lymphocytes; the protein content is always elevated, often to very high levels. Froin's syndrome (xanthochromic spinal fluid which clots on standing) may be present.

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ous system; when this is present, the disease is meningoencephalitis or meningomyeloencephalitis.

A large variety of agents are responsible for the syndrome of aseptic meningitis. All of the viral meningitides fall into this category; however, bacteria, leptospira, spirochetes and parasites may also produce it. Listed below are most of the possibilities that must be considered when aseptic meningitis is observed.

1. Healing bacterial meningitis—as the spinal fluid im-improves spontaneously or under the impact of therapy, the organisms disappear, the sugar level returns to normal, and lymphocytes outnumber neutrophiles.
2. Tuberculous meningitis
3. Multiple embolization to the brain in the course of bacterial endocarditis, especially the subacute variety.
4. Pertussis encephalopathy
5. "Serous" meningitis of scarlet fever
6. Thrombophlebitis of lateral sinus secondary to otitis media.
7. Leptospiral meningitis
8. Mumps—this is a very common cause in some areas of the country and may be present without involvement of the salivary glands.
9. Poliomyelitis—non-paralytic
10. Coxsackie virus infection of the meninges
11. Meningitis due to enteric cytopathogenic human orphan (ECHO) viruses.
12. Lymphocytic choriomeningitis
13. Infectious mononucleosis
14. Infectious hepatitis—pre-icteric phase
15. Herpes simplex meningitis
16. Herpes zoster meningitis
17. Malaria—especially falciparum variety
18. Brain abscess without localizing manifestations
19. Trichinosis

vomiting constitute the so-called "gastric crises", which are observed in about 10 per cent of cases. Ataxia, characterized by slapping of the feet and walking on a broad base, a positive Romberg sign, and diminished or absent vibratory and position sense are other neurologic features. The joints are often hyperextensible. A painless punched out ulcer at the base of the great toe—mal perforant—may be present. Postural hypotension is striking in some cases. Fifty to 60 per cent of patients have an autonomic bladder. Diplopia, ptosis of the eyelids, and Argyll-Robertson pupils may be detected. Atrophy of the optic nerves appears in 10 to 15 per cent of tabetics; if untreated, blindness develops in 70 per cent within 3 years, and in 90 per cent within 5 years.

Paresis is characterized by several syndromes: (a) a simple dementia, (b) a grandiose form in which euphoria and ideas of grandeur are outstanding, (c) paranoia, (d) neurasthenia featured by a variety of vague complaints, and (e) simple depression.

The treatment of neurosyphilis, regardless of type or duration, is 600,000 units of procaine penicillin injected intramuscularly once daily for 15 days.

Aseptic Meningitis

Aseptic meningitis may be defined as a syndrome in which there are manifestations of infection, signs of meningeal irritation, and an abnormal spinal fluid (increased number of cells, many of which are lymphocytes, and normal or elevated protein) from which bacteria cannot be isolated by routine methods. In many instances, neutrophiles are predominant early but are soon replaced by lymphocytes. It must be stressed that a spinal fluid must not be regarded as sterile unless cultures have been made on Saboraud's and corn-meal agar and in anaerobic media. The diagnosis of aseptic meningitis should be made only if there is no evidence of involvement of the brain or other part of the nerv-

have been defined: Type I (Brunhilde), Type II (Lansing), and Type III (Leon). Infection with one type does not protect against invasion by another. The virus grows well in tissue culture, and has been cultivated in cultures of human and monkey kidney cells, Hela cells, and human amnion, in all of which it produced cytopathic changes.

Virus is present in the stool and oropharynx of patients with poliomyelitis regardless of the clinical type of disease. It is recoverable from pharyngeal secretions for only a few days, but is demonstrable in the feces for several weeks. The intestinal tract is probably the main source from which virus is disseminated. The mode of infection is, therefore, fecal-oral—the same as that in salmonellosis, shigellosis, and other enteric infections. Very small quantities of stool contain thousands of infective doses of poliomyelitis virus. Poliomyelitis is as highly communicable as measles or chickenpox; in individuals under 15 years of age, infection with or without clinical manifestations occurs in 100 per cent of household contacts and 87 per cent of daily contacts.

The most important factor conditioning susceptibility to poliomyelitis is type-specific neutralizing antibody. Previous inapparent infection and illness without invasion of the nervous system are common in areas where the paralytic form of the disease occurs Many children and most adults possess neutralizing antibody for all 3 types of virus. Infants under 3 to 6 months old rarely get poliomyelitis because immunity is passively transferred from the mother. Babies born to women in the acute phase of poliomyelitis may develop the disease shortly after birth, indicating in utero infection or exposure during delivery. Among children, males are affected more often than females; the opposite is true in adults Pregnancy increases the risk of clinically apparent poliomyelitis. Multiparous females are more susceptible than primiparas. Menstruation or ovulation appear to heighten susceptibility. Absence of the tonsils and adenoids, regardless of the time of their removal, is associated with a marked

20. Syphilitic meningitis
21. Rheumatic fever
22. Tumors
23. Drugs, such as anesthetics, administered intrathecally producing a sterile inflammatory reaction.
24. Cerebral thrombosis
25. Multiple sclerosis
26. Allergic reactions involving the nervous system.

As can be seen from this long list, the etiology of this syndrome is often very obscure. Very important in arriving at a working diagnosis is a carefully taken history concerning the preceding illness, contact with animals or other vectors of disease, mode of onset of the meningeal manifestations, geographic location of the patient, and exposure to drugs and other agents. The possibility that a treatable infection is responsible for the spinal fluid changes must always be considered. Thus, it is well to rule out such diseases as tuberculous meningitis, subacute bacterial endocarditis, syphilis, leptospiral meningitis, trichinosis and malaria, for example. All of the viral meningitides fall into the category of aseptic meningitis; the most common causative agents observed in this country are the viruses of Coxsackie disease, mumps, and poliomyelitis. Since there is no specific therapy for these, delay in establishing their presence is of little practical significance. As a rule, in most viral meningitides diagnosis is made in retrospect on the basis of changes in antibody titers of acute and convalescent serums. The diagnostic procedures of value in most of the virus infections included in the table are described in the chapters of this book dealing with these infections.

Poliomyelitis

Poliomyelitis is a *common* acute viral infection which occurs only in man. Three antigenically distinct types of virus

f meningeal irritation, and abnormalities of the spinal fluid. The prodrome is characterized by one of the "minor" illnesses and is usually present for several days before the onset of other signs; it may be entirely absent. Varying degrees of meningeal irritation are present. The tripod and Hoyne's sign are not diagnostic; they merely indicate irritation of the meninges and are often observed in cases of bacterial meningitis. The spinal fluid usually contains between 25 and 500 cells, rarely as many as 1,000 to 2,000. Very early in the disease, there is often a preponderance of neutrophiles (up to 80 per cent); within a few days, however, lymphocytes become predominant. The protein is usually normal or only slightly elevated at the beginning of the illness, but may increase to between 50 and 100 mg. per 100 ml. The sugar content is normal or moderately elevated. Spinal fluid chloride reflects the plasma chloride level. These findings are the same as those observed in many types of aseptic meningitis and are not diagnostic of poliomyelitis. Viral and immunologic studies suggest that less than 40 per cent of cases of clinically diagnosed nonparalytic poliomyelitis are actually this disease.

The course of non-paralytic poliomyelitis is entirely benign. Defervescence usually occurs in 3 to 5 days, but meningeal irritation may persist for as long as 2 weeks beyond this. No changes in reflexes or muscle or cranial nerve function are detectable. The white blood count which may be elevated to 10,000 to 15,000 in the early stage of the disease is usually normal within one week. The spinal fluid often contains an increased number of cells (predominantly lymphocytes) and elevated protein for 2 to 3 or more weeks after the onset of the disease.

Paralytic Poliomyelitis: The syndrome of paralytic poliomyelitis consists of prodromal manifestations ("minor illness"), signs of meningeal irritation, abnormal spinal fluid, and involvement of various portions of the spinal cord, brain, or cranial nerve nuclei resulting in paresis or paralysis of

increase in incidence of bulbar poliomyelitis. Chilling or physical extertion of moderate to severe degree after invasion by the virus leads to more frequent development of paralytic poliomyelitis, especially in adults.

The incubation period of poliomyelitis varies from 3 to 35 days; about 80 per cent of cases occur within 6 to 20 days after contact with the virus. Four types of clinical pictures may develop: (1) *Inapparent infection.* (2) *"Minor illness."* (3) *Non-paralytic poliomyelitis.* (4) *Paralytic poliomyelitis.*

Inapparent Infection: In families in which a clinically recognized case of poliomyelitis is present, other susceptible members usually develop inapparent infection. The bulk of poliomyelitis (95 per cent) occurs in this form. There are no manifestations of illness, but the virus is present in the pharynx and intestine. It is probably also present in the blood. Type-specific neutralizing antibody usually develops.

"Minor Illness": The entire course of poliomyelitis may consist of a minor, non-specific illness lasting for several days, and without clinical or laboratory evidence of central nervous system invasion; this is "abortive" poliomyelitis. Three syndromes have been observed: (a) upper respiratory manifestations consisting of fever of varying degree, pharyngeal discomfort, with or without coryza, and reddening and swelling of the lymphoid tissues of the throat; (b) gastrointestinal disturbances with nausea, vomiting, diarrhea or constipation, and abdominal discomfort, accompanied by a moderate elevation of temperature; and (c) "grippe"-like disease with fever and generalized aching of muscle, bones, and joints, resembling mild to moderately severe influenza. Virus can be demonstrated in the pharynx, feces and blood in the early stages of these "minor" illnesses. Type-specific neutralizing and complement-fixing antibodies are present in the convalescent phase.

Non-Paralytic Poliomyelitis: Non-paralytic poliomyelitis is a syndrome composed of prodromal manifestations, signs

some, it becomes widespread within 48 hours. Rarely, a rapidly ascending paralysis of the Landry type is observed. Age is important in conditioning the extent of involvement. Infants less than one year of age are subject to very extensive disease. In children under 5 years old, paresis of one leg is most common. In patients between 5 and 15 years of age, weakness of one arm or paraplegia are most frequent, while in adults (16 to 65 years old) quadriplegia is observed most often. Dysfunction of the urinary bladder is at least 10 times more frequent in adults than in children. Paralysis of the muscles of respiration is most common in those older than 16 years of age. Among adults, men develop quadriplegia, respiratory paralysis, and loss of bladder function more frequently than women. Pregnancy does not increase the severity of the disease unless parturition takes place during the acute phase. There is a definite association of inoculation of antigenic materials ("triple vaccine," for example) with an increased risk of involvement of the muscles around the site of injection.

The location of muscle weakness depends on the portion of the spinal cord affected. Isolated infection of the cervical, thoracic, or lumbar areas may be present, or two or more parts of the cord may be involved simultaneously. The lumbar area is the one most frequently damaged. "Skip" areas, with disease in isolated segments of the various divisions of the cord, are often observed. The abdominal reflexes disappear early. Later, those in the extremities vanish as paralysis appears. Fasciculation of muscles about to become paralyzed is observed frequently. Paralysis of the arms, legs, trunk, back, and muscles of breathing occur in this type of poliomyelitis. Paralysis of the urinary bladder develops in about one-third of adults and usually accompanies weakness of the legs. An extensor plantar response (positive Babinski) is not an uncommon finding during the first one or two days; persistence or late development of this reflex is incompatible with poliomyelitis. Hyperesthesia of the skin is

various muscles. Damage may be present in parts of the nervous system other than anterior horn cells; the pre-central gyrus, the reticular formation in the medulla, the roof nuclei and vermis of the cerebellum, Auerbach's and Meissner's plexuses, and sympathetic ganglia may be involved. Not infrequently, there is a lack of correlation between the anatomic changes and the clinical findings. "Skip" areas are common in spinal paralytic disease; for example, involvement of the cervical and lumbar cord is often present with no dysfunction of the thoracic portion.

Prodromal manifestations are not infrequently absent in paralytic poliomyelitis. In some cases, the illness is biphasic in character. In these, the disease starts with fever and manifestations of one of the "minor" illnesses. After several days, all symptoms disappear but in from 5 to 10 days there is recrudescence of fever, the development of signs of meningeal irritation, and the appearance of paralysis. The commonest prodromal symptoms in adults are generalized muscle and bone discomfort. In children, upper respiratory tract syndromes are most frequent. Signs of meningeal irritation are present but may be incomplete. The spinal fluid findings in paralytic poliomyelitis are the same as those in the nonparalytic disease. The number of cells and quantity of protein in the spinal fluid bear no relationship to the severity of involvement and prognosis. The spinal fluid may remain entirely normal during the course of disease in about 0.1 to 0.2 per cent of cases.

Spinal Paralytic Poliomyelitis: In the early stages of spinal paralytic poliomyelitis, cramping pain in the muscles innervated by the affected neurones and hyperesthesia of the skin overlying them are present. The discomfort may be very severe; muscle "spasm," the exact mechanism of which is not clear, is usually detectable. Paralysis may not appear for some time after the onset of nervous system manifestations. In some instances, increase in muscle weakness is very slow; in others, it develops with moderate speed, while, in

nerve palsies, total external ophthalmoplegia, pupillary disturbances, Horner's syndrome, and hippus may occur. There may be unilateral or bilateral involvement of the 5th nerve with *difficulty in chewing and closing* the mouth, as well as deviation of the jaws. Paralysis of the 7th cranial nerve is common and usually unilateral. It is most often of the central type; the entire face or only the upper or lower parts may be affected. Disturbances of vestibular function and deafness result from damage to the nucleus of the 8th nerve.

Lower Cranial Nerve Nuclei—N 9,10,11,12. Life may be endangered when function of the 10th nerve is impaired, since swallowing is controlled by the combined action of N 10, 11, and 12. With involvement of these nerves, the voice has a nasal quality and movement of one or both halves of the soft palate is decreased or absent. Hoarseness and laryngeal stridor follow weakness or paralysis of the vocal cords. Unilateral or bilateral weakness of the tongue, sternocleidomastoid, and trapezius muscles may be present. Inability to swallow results in pooling of saliva and food in the pharynx with obstruction to the airway. Aspiration of fluid into the larynx, *reflex spasm of the glottis, and abductor paralysis* of the vocal cords constitute very serious threats to life.

Disease of the medullary respiratory center produces *irregularity of the rhythm, depth, and rate of breathing.* The thoracic muscles and diaphragm are not weak, unless spinal involvement is present Hiccoughing is frequent in the early phase of respiratory center dysfunction. *Hypoxia*, without visible cyanosis, is common and contributes to the intensity of the manifestations. In the late stages, cyanosis, unresponsive to oxygen administration, is commonly present, and the temperature, pulse rate and blood pressure are elevated. The final event is usually shock which, in the majority of cases, is irreversible despite the most heroic measures.

The manifestations of involvement of the circulatory regulating center are a deep cherry red color of the lips, flushed

frequent; increased vibratory sensation may be detected by special technics. Sensory loss does not occur. Constipation, abdominal cramps, and meteorism are common in spinal paralytic poliomyelitis and are due to partial ileus resulting from involvement of the autonomic nervous system and weakness of the abdominal muscles. When the disease is severe, sympathetic nervous system disturbances with tachycardia, hypertension, abnormal sweating, and cyanosis and coldness of the involved extremities (not due to superficial vasospasm) are present.

Fever is usually present in spinal paralytic poliomyelitis for the first few days and then disappears by gradual lysis. In 90 per cent of cases, there is little or no extension of paralysis after defervescence has been established for about 48 hours. In the remaining 10 per cent, however, progression of weakness may continue for as long as a week and be of notable degree.

Bulbar Poliomyelitis: The incidence of bulbar poliomyelitis differs from one epidemic to another and varies between 6 and 25 per cent. It occurs in 85 per cent of patients subjected to tonsillo-adenoidectomy within 30 days of onset of the disease and in those in whom this operation was carried out even many years before. Pure bulbar involvement (without any spinal cord signs) is commonest in children; adults with bulbar disturbances usually have associated spinal paralyses. The prodromal manifestations of bulbar poliomyelitis are often the same as in the spinal form. The syndromes which develop depend on the area of the brain stem involved, and result from damage to the medulla, pons, or midbrain. Signs and symptoms are produced by (a) dysfunction of the upper cranial nerve nuclei, (b) damage to the lower cranial nerve nuclei, and (c) disturbances of the respiratory and vasomotor regulating centers in the medulla. Combined bulbar and diffuse or focal encephalitis or spinal involvement may occur.

Upper Cranial Nerve Nuclei—N 3,4,5,6,7,8. Isolated ocular

Medical Complications of Paralytic Poliomyelitis

Paralytic poliomyelitis, especially in adults, often presents a number of serious and potentially lethal complications. These occur most frequently when the respiratory muscles are involved or when bulbar and bulbospinal disease is present. They include disturbances in water and electrolyte balance, electrocardiographic abnormalities, myocarditis with cardiac failure, hypertension, phlebothrombosis of the legs, dilatation of the stomach and large bowel, paralytic ileus, multiple erosions in the gastrointestinal tract with bleeding, acute ulcers of the esophagus, stomach or duodenum, bacterial pneumonia, pyelonephritis, renal lithiasis, syndrome resembling rheumatoid arthritis, bed sores, and various psychoses. Shock or pulmonary edema, or both, are the terminal events in practically all fatal cases.

Management of Poliomyelitis

Cases of "abortive" poliomyelitis require no therapy except for "symptomatic" relief of the manifestations of the "minor" illnesses. Antibiotics are without value.

The treatment of non-paralytic poliomyelitis involves primarily the relief of the headache, pain in the back, and "spasm" of the legs. Rest in bed with the mattress supported by a board is helpful in reducing the back discomfort. The application of moist heat in the form of "hot packs" to the neck, back, and thighs produces considerable relief. Analgesics such as Demerol and codeine are very useful, morphine derivatives are best not given. Neuromuscular examination should not be carried out more often than every 3 to 4 days. Bed rest is terminated as soon as severe discomfort is absent in order to reduce the risk of phlebothrombosis and pulmonary embolism. Every patient thought to have non-paralytic poliomyelitis should have orthopedic follow-up study 2 to 3 months after recovery.

florid appearance of the skin, a very rapid, irregular pulse, small pulse pressure even when the blood pressure is normal, and moderate to severe hypotension. Hyperthermia, cold mottled clammy skin, shallow respiration, anxiety, restlessness and confusion appear as the circulatory mechanism becomes progressively more impaired and untreatable shock develops.

Polio-encephalitis. Encephalitic symptoms, focal or diffuse, may occur separately or together with bulbar and spinal poliomyelitis. The diffuse form is characterized by anxiety, apprehension, a feeling of impending doom, and rapid succession of ideas racing through the mind. Twitching and jerking motions of the facial muscles and extremities and flushing of the face occur. Insomnia may be severe. In fatal cases, confusion is marked and progresses to lethargy and death. Somnolence may be the outstanding feature and continue until death or recovery takes place. In focal polioencephalitis there may be visual-verbal agnosia, myoclonic jerks, grand mal convulsions which occasionally persist for a long time after recovery, spastic hemiparesis, ataxia of one arm or leg, and hydrocephalus.

The diagnosis of paralytic poliomyelitis can usually be made on clinical grounds. The outstanding manifestations are a lower motor neurone lesion with flaccid weakness and hypo- or areflexia. Signs of upper motor neurone disease or decreased sensation are not compatible with poliomyelitis. The only positive method of establishing the diagnosis of paralytic poliomyelitis is isolation of the virus from the stool or pharyngeal secretions (spinal cord or brain at necropsy) or demonstration of a rise in the level of neutralizing antibody to the isolated strain in acute and convalescent phase serums. If virus cannot be isolated, the 3 type strains maintained in tissue culture may be used. One attack of poliomyelitis usually confers immunity for life against the responsible serotype.

lungs of exudate (the opening in the trachea permits easy toilet of the lower airway), (3) repeated bouts of major degrees of pulmonary atelectasis requiring tracheal catheterization or bronchoscopy, and (4) inability to keep the airway relatively free of secretions (this is often purely a matter of availability of a sufficient complement of experienced personnel).

Decreased movement of the diaphragms or intercostal muscles, or both, indicates the need for frequent determination of vital capacity. When this is reduced to 50 per cent or less than normal, on the basis of age and weight, artificial respiration with a tank or cuirass-type chest respirator must be given. The level of negative pressure employed must be set at that which produces a normal tidal volume as measured with a respirometer. The speed of respiration is adjusted from 12 to 16 per minute, and is altered, if necessary, to suit the comfort of the patient. Determination of plasma CO_2 content and arterial oxygen saturation should be made as frequently as possible; this is especially important when bulbar disease with pooling of secretion is present, because considerable hypoxia may develop before cyanosis is apparent. Oxygen should be administered to all cases. If hypotension is present, alternating negative and positive pressures of equal degrees often help in restoring normotension. The chest respirator or rocking bed cannot be substituted for the tank respirator in the acute phase of the disease. The electrophrenic respirator is of no value in the management of paralysis of the muscles of respiration because the phrenic nerves fail to respond to stimulation within 24 to 36 hours following onset of the disease as a result of rapid axonal degeneration. The prophylactic use of antimicrobial agents to prevent secondary bacterial infections in cases of bulbar and respiratory muscle paralysis, with or without tracheostomy, is not beneficial and may, in fact, be potentially dangerous. "Weaning" from the tank respirator should

The management of paralytic poliomyelitis involves (a) the use of all measures to spare the life of the patient threatened by involvement of vital areas, (b) relief of discomfort, (c) maintenance of weak muscles in as good a condition as possible until normal neuronal function has sufficient time to return, (d) immediate recognition and treatment of medical complications, (e) prophylaxis and therapy of emotional disorders, (f) surgical treatment of correctable defects, and (g) social, economic, occupational, and physical rehabilitation.

Patients with paralysis of swallowing, loss of function of the breathing muscles, pulmonary edema, or shock are in great danger of death. Dysfunction of N 9 and 10 leads to complex problems of infection and regulation of caloric, water, and electrolyte balance but is most serious because of the danger of fatal obstruction of the airway. For this reason, it has been suggested that tracheostomy be performed in all such cases. This operation is followed, however, by a much higher incidence of bronchopulmonary infection than occurs when the procedure is not carried out. The preferred initial management of swallowing difficulty is postural drainage, suction to keep the hypopharynx as free of fluids as possible, and maintenance of adequate intake of food and water by nasogastric intubation. The prone position takes advantage of the normal forward inclination of the trachea as an aid to drainage. Elevation of the foot of the bed 2 to 3 feet from the floor also helps to keep fluids out of the lower respiratory tract. Most important is judicious suctioning of the throat carried out by an experienced physician or nurse. If, in addition, fluid and electrolyte are administered parenterally at first and later by gavage, most patients get into little or no difficulty. In some cases, however, tracheostomy does become necessary, despite the risks. The indications for this procedure are (1) abductor paralysis of the vocal cords which makes the operation mandatory, (2) pneumonia with inability to clear the

examinations should not be carried out too often in the acute phases of the disease in order to minimize the possible deleterious effect of exercise in increasing the degree of paralysis. Daily physiotherapy is usually started 3 to 4 days after complete defervescence has appeared and extension of weakness has stopped. Exercise against resistance, even that of gravity, is thought to be most beneficial by some clinicians. In many clinics, exercise in water to remove the effects of gravity is standard practice.

Maximal return of muscle function usually is established at the end of 2 years following the onset of paralytic poliomyelitis. The aid of the orthopedic surgeon should be enlisted after this time, and a program of surgical rehabilitation set in motion. Persistent coldness and cyanosis of the lower extremities suggests consideration of lumbar sympathectomy. Occupational and physical rehabilitation should be initiated as soon as possible.

The overall mortality rate for poliomyelitis is about 5 per cent. "Abortive" and non-paralytic cases recover completely. About 2 to 5 per cent of children and 15 to 30 per cent of adults with paralyzing infection die; the percentage increases directly with age. When bulbospinal involvement (especially with medullary or phrenic and intercostal nerve dysfunction) is present, the fatality rate varies between 25 and 75 per cent; in these cases, it is greatly influenced by age, the presence of shock, pulmonary edema, superimposed infection, or other medical complications.

Many cases of paralytic poliomyelitis recover completely. In a considerable number, there is return of muscle function to some degree. Only very few remain totally paralyzed. It is striking, though paradoxical, that the more life-threatening the disease in the acute stage, the more frequent is complete functional recovery, if the patient survives. Thus, paralysis of the respiratory center usually disappears completely. Dysfunction of N 9 and 10 is followed by total recovery in most instances, although mild palatopharyngeal

be started after the first day and increased as rapidly as possible.

The use of the electrophrenic respirator is indicated when the respiratory center is involved. Tank respiration may only increase the difficulty. Indirect stimulation of one phrenic nerve through the skin is usually sufficient. If the need for the electrophrenic respirator is continuous for several or more days, the phrenic nerve may be exposed and the electrode applied directly by means of a metal clip for as long as a week.

When pulmonary edema supervenes in patients receiving artificial respiration, the use of positive intratank pressure or positive pressure breathing through a cuffed tracheotomy tube may be helpful. Shock is easier to prevent than to treat. Assurance of adequate oxygen saturation, prevention of dehydration, and early treatment of superimposed bacterial infection, are of prophylactic value. When marked hypotension develops, vasoconstricting agents such as norepinephrine are often very helpful in establishing normotension. As a rule, however, these drugs finally become ineffective as their use is prolonged. Plasma infusions may be of some help. Hypotension appearing during artificial respiration may respond to alternating positive and negative tank pressures of approximately the same degree.

The relief of discomfort is one of the most important problems in the care of paralytic poliomyelitis. The measures employed include all those discussed in the treatment of the non-paralytic disease. Changing the position of paralyzed limbs and moving the patient about in bed are also very effective in reducing the frequency and intensity of pain. Weak muscles must be maintained in as good condition as possible until neuronal function returns; the time, degree, and extent of resumption of function is unpredictable, so treatment should be continued for at least 2 years. This aspect of therapy is best managed by the physiotherapist with a broad experience with p[illegible] Muscle

formalin-inactivated strains of the 3 viral serotypes grown in monkey kidney tissue culture. The vaccine is reported to be about 60 to 70 per cent effective against Type 1, and 85 to 90 per cent against Types 2 and 3. The recommended schedule of inoculation is 1 ml. initially, followed by 1 ml. 4 weeks and again 7 months after the first injection. No antibody is demonstrable in about 20 per cent of patients after the first injection. In most individuals without antibody prior to vaccination, neutralizing capacity of low degree appears in about 4 to 6 weeks after the first dose of vaccine, but falls gradually over the next few months. The second "booster" injection 7 months later produces a rapid rise in antibody to high levels. Persons immune to a single serotype when first inoculated develop a rapid increase in antibody to all 3 types. The vaccine does not appear to decrease the incidence of non-paralytic poliomyelitis. The duration of protection is unknown. Reactions to the vaccine are uncommon, headache, stiffness of the neck, arms, and legs accompanied by pain, skin hypersensitivity, fever, sore throat, vomiting, and pain at the site of injection have been noted. Approximately 1 to 3 paralytic cases of poliomyelitis appear to be associated with each million injections of vaccine.

Experimental studies suggest that the oral administration of living virus vaccines also produces neutralizing antibodies and protection against infection. The particular strains of poliomyelitis virus used are capable of growing in the intestinal tract but do not invade the nervous system. Adequate field trials have not yet been carried out. Although promising, judgement of the degree of effectiveness of this type of vaccine must be reserved.

Tetanus

Tetanus is uncommon in the United States although it occurs with considerable frequency in some parts of the

weakness may occasionally persist for life. Paralysis of the muscles of respiration often disappears completely. In some cases the final vital capacity, although reduced, is adequate to maintain ventilation, even with moderate physical exertion. In a very few instances is chronic respirator care necessary. Weak extremities regain about 60 per cent of the total strength that they will ever recover in 3 months, and 80 per cent within 6 months. Improvement may continue for as long as 2 years. The final degree of functional return depends on the number of neurones totally destroyed, and varies from as low as zero to as high as 100 per cent.

Because 90 to 95 per cent of cases of poliomyelitis are inapparent or "minor" infections and are not diagnosed, the prevention of the disease by isolation is very difficult and probably not practical. Contact with known cases should be avoided. Restriction of community activities such as swimming, gathering of people, etc., is not necessary except with large epidemics when it is more effective in allaying panic than in reducing infection. Pregnant women should take special precaution because of the increased susceptibility to the disease. Tonsillectomy is contraindicated in areas where poliomyelitis is present. All individuals with "minor" illnesses during the poliomyelitis season should limit their physical activity and avoid chilling until all symptoms have disappeared.

The use of gamma globulin prepared from pools of normal human plasma has not been strikingly effective as a prophylactic measure in either family or outside contacts. However, in persons peculiarly susceptible such as pregnant women, or physicians and nurses accidentally in contact with virus-containing materials, the administration of gamma globulin may be worthwhile. The dose is 0.15 ml. per pound of body weight; the maximal quantity for adults is 20 ml.

Active immunization against paralytic poliomyelitis has been successfully produced by parenteral ad[illegible]

Cephalic Tetanus: This follows injuries to the face or *otitis media*, and is *characterized* by paralysis of the facial nerve, in addition to trismus and other signs of generalized tetanus.

The diagnosis of tetanus is made on clinical grounds. A history of a wound followed by the onset of any of the manifestations described above should suggest this disease. It must be kept in mind, however, that trismus may be absent or, when present, may be due to a variety of other causes including infected teeth, trichinosis, mumps, infection in the mouth, lymphadenitis in the parotid area or at the angle of the jaw, etc The tetanic seizures may be produced by strychnine. Bacteriologic study of the wound may be of help in some cases. However, the site of injury may be completely healed by the time tetanus appears. Nonpathogenic anaerobes may have the same morphologic appearance as *Cl. tetani.* Whenever possible, cultures of the wound should be made in anaerobic media and the pathogenicity of the organisms proved by injecting culture filtrates (toxin) into mice.

The following are the items of importance in the treatment of tetanus:

(1) Surgical debridement of the wound with a zone of normal tissue around it is recommended.

(2) Antitoxin: 50,000 units is administered intramuscularly followed by 50,000 units intravenously after appropriate skin and eye tests for serum sensitivity.

(3) Tracheotomy: Since many deaths are due to laryngospasm, this operation is an important prophylactic measure.

(4) Sedation: Any type of sedative including the barbiturates, chloral hydrate, or paraldehyde may be used. They should be administered in quantities sufficient to keep the patient drowsy but still arousable. Sedation should be given on the basis of need and not on a rigid schedule, which may lead to overdosage and poisoning. Magnesium

world. It is not an infection of the nervous system since organisms are never found there. The disease results from the effect of toxin elaborated by organisms growing in a wound. Whether the toxic substance reaches the nervous system by way of the blood stream or in direct nerve transmission is still a matter for debate.

Tetanus follows the introduction of spores of *Clostridium tetani* into wounds contaminated by soil or objects on which the organisms happen to be present. It may follow animal bites, the sting of a bee, or even a very minor wound. Although penetrating injuries are said to be most commonly involved, a large number of cases follow minor injuries. The incubation period is variable, it may be as short as 1 day or as long as 2 months; it averages 3 to 21 days.

Three clinical forms of tetanus have been described.

Local Tetanus: Spasm of the muscles in the area of injury is very common, pain is usually associated with this finding and may be quite severe. This form of the disease is generally overlooked, although diagnosis and immediate treatment at this time might be effective in preventing the appearance or decreasing the severity of the generalized form.

Generalized Tetanus: Trismus is the hallmark of this form of the disease; although usually bilateral, it may initially be limited to one side and is entirely absent in about 25 per cent of cases. Marked stiffness of the neck, back and hamstring muscles may be present and suggest the possibility of meningitis; the spinal fluid is, however, entirely normal. The abdominal muscles may become so rigid as to suggest severe peritonitis. Risus sardonicus may be noted. Hyperirritability and the tendency to seizures are outstanding. The slightest stimulus or noise may produce a sudden tetanic episode which may lead to death. Laryngeal and glottal spasm occur in the severe cases and may appear spontaneously or be induced by the sight of food or water (hydrophobia).

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sulfate has been used with good effect but great care must be exercised not to produce respiratory arrest; if this occurs, it can be quickly reversed by the intravenous injection of calcium gluconate.

(5) Muscle-relaxing agents: Mephanesin and succinyl choline chloride may be used to prevent convulsions and produce relaxation. Paralysis of the diaphragm may occur but eventually disappears; treatment with a tank respirator is indicated temporarily in this situation.

(6) No food or water by mouth: Electrolyte and water balance must be maintained by intravenous hydration. A polyethylene nasogastric tube may be inserted after several days and a balanced liquid food mixture administered.

(7) Penicillin (crystalline G): 250,000 units is given intramuscularly every 6 hours for 10 days.

(8) Constant nursing care with attention to skin, bladder and bowels is essential.

(9) The frequency of necessary procedures should be limited; it is the writer's practice to arrange for all manipulations, nursing care, medications, etc., to be carried out when the penicillin injections are given; in this way, the patient is disturbed only 4 times a day. Sedation should be adequate at these times.

(10) Absolute quiet in an isolated room is obligatory.

(11) Immunization with toxoid after recovery must not be neglected, since most patients are not immunized by the disease.

The prognosis is poor in tetanus. In most series the fatality rate is between 50 and 75 per cent; it may be reduced to as low as 20 per cent in favorable cases in whom the diagnosis is made early, and therapy instituted promptly. The closer the wound to the brain, the poorer the outlook; thus, face injuries followed by tetanus have a higher risk of death than those on the feet. The shorter the incubation period, the greater the possibility of a fatal outcome. The presence of fever when no secondary infection is present is

also a bad prognostic sign. Death is more frequent in very young and in old patients.

Tetanus is a preventable disease. The administration of 3,000 units of antitoxin is indicated in any suspicious wound. When the disease develops despite such prophylaxis, the incubation period may be quite prolonged and the outlook for recovery is improved. All people should be protected by the administration of tetanus toxoid. After the initial immunization, a booster dose of fluid toxoid (1 ml.) should be given 1 and 2 years later, and again when any injury occurs. In previously immunized individuals, the injection of 1 ml. of toxoid is an effective prophylactic, good "recall" of antibody occurs when a "booster" is given as late as 10 years after the last injection. For wounds of the face or head, it is safest to give 3,000 units of antitoxin plus a dose of toxoid.

ENCEPHALITIS—GENERAL FEATURES

Inflammation of the entire brain or portions of it may occur as an isolated entity (encephalitis), or be accompanied by manifestations of involvement of the spinal cord (encephalomyelitis). In most instances there is also evidence of meningeal irritation. This disease may be produced by bacteria, viruses, rickettsiae spirochetes, yeasts and fungi, or other parasites. It also follows a number of systemic infections or may result from sensitization to such products as horse serum or bacterial vaccines

It has been pointed out that the outstanding feature of encephalitis is the absence of characteristic syndromes in association with specific etiology Thus, regardless of the cause of the disease, the clinical picture which develops is, in general, the same. In some types of encephalitis, however, certain manifestations are more frequent than in others and may be of help in making a presumptive diagnosis. The syndrome of encephalitis is composed of signs of infection, evidence of meningeal irritation, abnormal spinal fluid, and

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mals or their products, (c) any type of illness preceding the appearance of encephalitis by one month or less, (d) injections of any kind, and (e) mode of onset and features of the early course of the encephalitis. This type of information often directs attention to a specific cause and permits a presumptive etiologic diagnosis.

(2) *Physical examination* may reveal abnormalities which, in addition to those in the nervous system, may suggest the specific etiology. Thus, the presence of cardiac murmurs plus fever and leucocytosis may raise the question of subacute bacterial endocarditis with focal embolic encephalitis. Periorbital edema, swollen tender muscles and a neurologic syndrome require consideration of trichinosis.

(3) *Laboratory studies* should include blood cultures, electrocardiograms (abnormal in some cases of trichinosis and in encephalomyocarditis), white blood count, chemical and bacteriologic studies of spinal fluid, lung x-rays, biopsy in certain instances, and other specific investigations that may be indicated by certain situations.

(4) *Virologic and serologic studies* are of greatest importance in establishing the etiology of encephalitis. Isolation of a specific virus is usually not practical, because methods for accomplishing this are not available in routine hospital laboratories. Furthermore, some of the viruses cannot be recovered from the spinal fluid and are obtained only from the brain and spinal cord after death. The most useful method of establishing the etiology of a viral encephalitis is by serologic study; serums obtained in the acute and convalescent phase (2 to 4 weeks after onset) must be compared. The procedures of value in specific infections are discussed below.

The physician must constantly keep in mind the fact that some forms of encephalitis, specifically those secondary to bacterial infection, are treatable with antimicrobial agents. These must be recognized early and therapy instituted

manifestations indicating local or diffuse involvement of the brain or spinal cord, or both. The following are the clinical features which may be observed, although not all of these are present in every case.

(1) Signs and symptoms of infection include fever, chills in some instances, malaise, headache, nausea, and vomiting. The white blood count may be normal or elevated.

(2) Evidence of meningeal irritation is characterized by stiff neck, stiff back, positive Kernig sign, and abnormal spinal fluid. In most cases, the fluid contains an increased number of cells (rarely more than 1,000/mm^3) most of which initially are neutrophiles but subsequently are lymphocytes. There is an increased protein and a normal or somewhat elevated sugar level. The spinal fluid may be entirely normal in a rare instance.

(3) Manifestations of damage to the brain or spinal cord, or both, may be evidenced by (a) focal seizures or aphasia (cortex), (b) extensor plantar response, hyper-reflexia, and spastic paralysis (upper motor neurone), (c) rigidity, tremor, chorea, or athetosis (basal ganglia), (d) nystagmus, intention tremor, muscle hypotonicity, and adiadokokinesis (cerebellum), (e) levels of sensory loss or defects in position and vibratory sense (spinal cord), and (f) urinary bladder paralysis, ileus, hypertension, tachycardia, and abnormal sweating (autonomic nervous system).

In some patients, the encephalitis is so mild that it produces few or no signs or symptoms, and its presence is diagnosed only retrospectively by means of serologic studies. In the clinically apparent cases the diagnosis is made when the findings described above are present. The etiology is frequently not revealed by the clinical picture and can be ascertained only on the basis of one or more of the following studies:

(1) *Carefully obtained history* as to (a) geographic location of the patient, (b) exposure to insects and various ani-

Trichina Encephalitis

Encephalitis may occasionally complicate trichinosis. The diagnosis is suspected on the basis of other manifestations of the disease and the presence of eosinophilia, although involvement of the brain may develop prior to the appearance of an elevation of the number of eosinophiles in the circulating blood (Chapter XIV). The spinal fluid is often normal except for an increased protein content.

Toxoplasmosis

Encephalitis due to invasion of the brain by *T. gondii* is primarily a problem in very young children. The diagnostic points are (a) convulsions, (b) intracranial calcifications, and (c) chorioretinitis. There is no specific treatment.

Viral Encephalitis

A number of viruses are responsible for encephalitis or encephalomyelitis. Space does not permit an exhaustive discussion of each. Below are described the salient clinical features, epidemiologic backgrounds, diagnostic procedures, and methods of therapy and prevention of the encephalitides which have been observed in the United States.

Rabies

Rabies follows the bite of rabid cats, dogs, foxes, skunks, wolves, and some species of bats Contamination of a skin abrasion with the saliva of such animals may also lead to the development of the disease. The incubation period averages 1 to 3 months but may be as short as 10 days or as long as a year. The closer the site of the wound to the

promptly. There is no effective treatment for any of the viral encephalitides; for this reason the delay in making a specific diagnosis necessitated by serologic tests is of no importance in affecting the outcome of the disease.

Bacterial Meningoencephalitis

Encephalitis may occur during the course of bacteremia due to various organisms. It is not rare with subacute bacterial endocarditis and is due to the presence of multiple cerebral emboli producing focal encephalitis. Brain abscesses and purulent meningitis are uncommon except when acute endocarditis is present. Involvement of the brain may also occur as a complication of bacterial meningitis. These types of encephalitis are treatable with antimicrobial agents, the drug used depending on the sensitivity of the organisms.

Mycotic Meningoencephalitis

Torula, Candida (Monilia), various fungi but especially *Mucor, Histoplasma capsulatum,* and *Coccidiodes immitis* may be responsible for encephalitis. Specific diagnosis is made by isolation of the organisms from spinal fluid or brain on Saboraud's medium or corn meal agar. When *Torula* is involved, treatment with Amphoterian B is worth a trial; the method is described in Chapter VII in the section on mycotic pneumonia.

Rickettsial Encephalitis

Encephalitis may occur in the course of typhus fever. It is due to *R. prowazeki,* is usually detected because of the other features of the disease of which it is a part, and responds to the same therapy which produces cure of the other manifestations (Chapter XVI).

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Encephalitis due to invasion of the brain by *T. gondii* is primarily a problem in very young children. The diagnostic points are (a) convulsions, (b) intracranial calcifications, and (c) chorioretinitis. There is no specific treatment.

Viral Encephalitis

A number of viruses are responsible for encephalitis or encephalomyelitis. Space does not permit an exhaustive discussion of each. Below are described the salient clinical features, epidemiologic backgrounds, diagnostic procedures, and methods of therapy and prevention of the encephalitides which have been observed in the United States.

Rabies

Rabies follows the bite of rabid cats, dogs, foxes, skunks, wolves, and some species of bats. Contamination of a skin abrasion with the saliva of such animals may also lead to the development of the disease. The incubation period averages 1 to 3 months but may be as short as 10 days or as long as a year. The closer the site of the wound to the

brain the shorter the incubation period. Prodromal manifestations consist of fever, headache, anorexia, nausea, vomiting, and sore throat. These last for 2 to 4 days and are followed by a picture of increasing irritability characterized by restlessness, anxiety, and insomnia; all of these symptoms may be replaced by depression. Most patients have pain, hypesthesia, or paresthesias in the area of the wound. As the disease progresses, the outstanding manifestations are hyperactive reflexes, muscle hypertonicity, tachycardia, pupillary dilatation, hypersensitivity to external stimuli, and increasing agitation and apprehension. Muscle twitchings may appear and be followed by generalized convulsions. Hydrophobia—painful and severe laryngospasm on attempted swallowing or the sight or sound of fluids—is present; each episode may be accompanied by difficulty in breathing and cyanosis. Behavior may be wild and destructive but attempts at biting are rare. Patients usually die within 3 days of onset of the excitement phase. If they survive longer, death is preceded by paralyses, apathy, or coma. The spinal fluid may be normal or contain up to 100 cells. The peripheral white blood count varies between 20,000 and 30,000. The fatality rate in rabies is 100 per cent. There is no effective therapy.

Treatment of the local wound is imperative in every situation. Cleansing with concentrated green soap solution or 1 per cent zephiran chloride solution is effective when carried out early. The application of fuming nitric acid is questionable. The indications for immunization against rabies using Semple vaccine or the recently developed egg-grown one are given in detail in Table 1. It is best to give vaccine together with hyperimmune serum (0.5 ml. per Kg. of body weight). In ordinary cases, 7 to 14 daily doses of the vaccine are administered; with severe bite, this should be continued for 21 days. If it is possible to capture the animal responsible for the bite, it should be observed closely

for the development of signs of rabies. In questionable exposures, it is probably best not to actively immunize until some conclusion has been reached concerning the status of the responsible animal, because the injection of vaccine is accompanied by severe encephalitis (one case per 2,000 patients receiving the Semple preparation); the fatality rate of this complication is 25 per cent. One of the most effective ways of reducing the risk of rabies in man is the immunization of all dogs and cats.

Table 1

INDICATIONS FOR SPECIFIC POST EXPOSURE TREATMENT ‡

Nature of exposure	Condition of biting animal: At time of exposure	Condition of biting animal: During observation period of 10 days	Recommended treatment
I. No lesions, indirect contact only	Rabid		None*
II. Licks: (1) Unabraded skin	Rabid		None*
(2) Abraded skin and abraded or unabraded mucosa	(a) Healthy	Healthy	None
	(b) Healthy	Clinical signs of rabies or proven rabid	Start vaccine at first signs of rabies in animal
	(c) Signs suggestive of rabies	Healthy	Start vaccine immediately; stop treatment if animal is normal on 5th day after exposure**
	(d) Rabid, escaped, killed, or unknown		Start vaccine immediately
III. Bites: (1) Simple exposure	(a) Healthy	Healthy	None
	(b) Healthy	Clinical signs of rabies or proven rabid	Start vaccine at first signs of rabies in animal
	(c) Signs suggestive of rabies	Healthy	Start vaccine immediately; stop treatment if animal is normal on 5th day after exposure**
	(d) Rabid, escaped, killed, or unknown, or any bite by wolf, jackal, fox or other wild animal		Start vaccine immediately

Table 1 (*Continued*)

Nature of exposure	CONDITION OF BITING ANIMAL: *At time of exposure*	CONDITION OF BITING ANIMAL: *During observation period of 10 days*	*Recommended treatment*
(2) Severe exposure: (Multiple; or face, head, or neck bites)	(a) Healthy	Healthy	Hyperimmune serum immediately; no vaccine as long as animal remains normal
	(b) Healthy	Clinical signs of rabies or proven	Hyperimmune serum immediately; start vaccine at first sign of rabies
	(c) Signs suggestive of rabies	Healthy	Hyperimmune serum immediately, followed by vaccine, vaccine may be stopped if animal is normal on 5th day after exposure
	(d) Rabid, escaped, killed, or unknown Any bite by wild animal		Hyperimmune serum immediately, followed by vaccine

* Start vaccine immediately in young children and in patients where a reliable history cannot be obtained.

** An alternative treatment would be to give hyperimmune serum and not start vaccine as long as the animal remained normal.

Note: To be effective hyperimmune serum must be given within 72 hours of exposure Dose 0.5 ml. per Kg of body weight.

These indications apply equally well whether or not the biting animal has been previously vaccinated.

‡ Expert Committee on Rabies—World Health Organization on Technical Report Series, Geneva, 1954, No 82

St. Louis Encephalitis

This disease occurs most often in the late summer and early fall. Circumstantial evidence has incriminated Culex mosquitoes in its transmission, although a chicken mite has also been suspected. The reservoir of the virus is thought to be birds. The incubation period is 4 to 21 days. The fatality rate is approximately 25 per cent, being highest in young children and patients over the age of 50. Most individuals make a complete recovery, but between 5 and 10 per cent have neurological residua. Diagnosis is established by demonstration of an increase in complement fixing or neutralizing antibody in the blood of the patient. There is no specific therapy.

Equine Encephalitis (Eastern and Western)

Equine encephalitis occurs primarily in the summer and is a disease mainly of horses. Both *Aedes* and *Culex* mosquitoes are thought to be vectors of the virus. Birds, especially pheasants and pigeons, are thought to be intermediate hosts. The disease in man is thought to follow the bite of an infected mosquito. The clinical picture is that of diffuse encephalitis; cranial nerve palsies are thought to be uncommon. There is a peripheral leucocytosis which may be as high as 60,000. The spinal fluid contains up to 1,000 cells most of which are neutrophils. The eastern variety affects children more often than adults. The death rate has been reported as high as 50 per cent. There is no specific treatment. Vaccines have been devised but have not yet had an ample trial in human beings. The diagnosis is made by demonstration of a rising complement fixing or neutralizing antibody titer in the serum of patients.

Lymphocytic Choriomeningitis

Lymphocytic choriomeningitis is characterized primarily by signs of meningitis. A severe encephalitis or encephalomyelitis is present, in addition, in some cases. The disease is produced by a virus and is endemic in the house mouse from which it is transmitted to man by contamination with nasal secretion, urine, or feces. The infection occurs most often in the late fall, winter and spring. The incubation period is 1 to 3 days. The initial manifestations in most cases are suggestive of a respiratory tract infection with cough and sore throat. These usually clear in a few days to 2 weeks, only to be followed 1 to 4 days later by fever, and signs of meningeal irritation. In many patients the entire disease does not go beyond this, although conjunctivitis, photophobia, abdominal pain, and backache may be present. Rarely, involvement of the brain or spinal cord occurs and produces a picture of encephalitis or encephalomyelitis indistinguishable from that due to other viruses. The spinal fluid may contain as high as several thousand cells, 95 to 100 per cent of which are lymphocytes; in some cases, 20 per cent may be neutrophiles. Neurologic residua such as paralysis or Parkinsonism may be present after recovery. The diagnosis is made on the basis of a rising complement fixing antibody titer (positive by the 3rd to 4th week) or by the demonstration of an increase in neutralizing antibodies (significant 7 to 8 weeks after onset of infection). There are no specific therapeutic or prophylactic measures.

Infectious Mononucleosis

Encephalitis or encephalomyelitis rarely complicates the course of infectious mononucleosis. The clinical pictures cannot be differentiated from other forms of viral infection of the brain or spinal cord. The disease may be very ex-

tensive and rarely produces death. There is no specific therapeutic measure. The diagnosis of infectious mononucleosis has been discussed in Chapter VI.

Herpes Simplex Encephalitis

Severe encephalomyelitis may be due to the virus of herpes simplex. This may follow a simple fever blister or diffuse infection such as is seen in Kaposi's varicelliform eruption (Chapter XV). There are no specific clinical features other than the presence of the skin lesions. The diagnosis is established by the demonstration of an increase in complement fixing or neutralizing antibody. There is no specific therapy.

Herpes Zoster Encephalitis

Encephalitis associated with herpes zoster is rare. Occasional cases with stupor and various paralyses have been described. The spinal fluid may be normal or reveal the features present in other virus infections of the nervous system. Diagnosis is usually made on the basis of the presence of the typical skin lesions. There is no specific therapy.

Acute Hemorrhagic Necrotizing Encephalopathy

Although the etiology of this type of encephalitis is unknown, it has been presumed to be due to a virus. The disease starts with manifestations of an upper respiratory tract infection or an influenza-like syndrome. After a period of well being for several days, signs of severe encephalitis appear. These consist of fever, severe confusion, coma, generalized convulsions, hemiplegia, or quadriplegia. The cerebrospinal fluid contains an increased number of cells, most of which are neutrophiles, and an elevated protein content; red blood cells are usually not present. There is often a

peripheral leucocytosis. Most cases end in death. There are no specific diagnostic procedures, and the nature of the disease is usually not defined except by autopsy study. There is no specific therapy.

Post-Infectious Encephalitides

Encephalitis or encephalomyelitis may complicate the course of measles, chicken pox, German measles, mumps, and smallpox vaccination. Although the exact mechanism of the neurologic involvement is not known, it is presently presumed to be due to a hypersensitivity reaction. The possibility of activation of a latent central nervous system virus has, however, not been excluded. Four main clinical syndromes may appear. (1) The most common one is diffuse cerebral involvement and is characterized by stupor or coma in most cases, or by severe generalized convulsion in some. (2) Localized cerebral signs, including athetosis, spastic paralyses, focal seizures, etc., may be present. (3) In some cases, the manifestations are limited to those of uni- or bilateral cerebellar involvement. (4) Uncommonly, a pure spinal cord syndrome with sensory changes may be observed. The spinal fluid changes are those of "aseptic" meningitis (see above).

Post-infectious encephalitis is commonest after measles, appearing in approximately 1 out of every 800 cases of this disease. It occurs in modified rubeola less frequently. The nervous system manifestations usually appear as the rash is beginning to fade, but may develop at any time, having been observed rarely even before the skin eruption appears. The fatality rate is approximately 15 per cent, most of the deaths occurring in the first 2 to 3 days. The risk of residual neurologic and psychological defects after recovery is approximately 65 per cent, these vary from very minor behavioral disturbances to complete organic deterioration. There may be a considerable latent period between recovery

from the acute phase of post-measles encephalitis and the appearance of residua. There is no specific prophylaxis or treatment. Although cortisone has been used, its effectiveness still remains to be proved. The administration of large doses of gamma globulin as a therapeutic measure has also been suggested; there is no evidence that it is effective.

Encephalitis occurs in approximately 1 out of every 10,000 cases of chicken pox. Although it may produce a variety of clinical pictures, it is striking that isolated cerebellar involvement is more common in this form than in any of the other post-infectious encephalitides. The outstanding signs are ataxia, nystagmus, and adiadokokinesis. The fatality rate is about 5 per cent. The frequency of residual defects is unknown, although a small number of patients do develop both psychological and neurological defects

German measles is complicated by encephalitis about once in every 35,000 episodes. The features are similar to those of the other post infectious encephalitides. Death is very uncommon, and residual defects are much less frequent than after measles or chicken pox. There is no specific treatment.

In the United States, one in every 350,000 people injected with cowpox vaccine for the first time develops encephalomyelitis. This is not observed in individuals who are revaccinated. The older the child, the greater the risk of post-vaccinial encephalitis. The incidence is higher in some countries being of the order of 1 in 2,000 primary vaccinations and 1 in 50,000 for revaccinations Symptoms of nervous system involvement usually appear from 10 to 12 days after vaccination, although they may develop as early as the second or as late as the twenty-fifth day. Papilledema and trismus have been observed. The fatality rate ranges from 30 to 50 per cent. If recovery occurs, there are usually no residua. There is no treatment. Vaccination before the age of 6 months, immunization only of individuals in good health, and avoidance of the procedure in patients exposed

to diphtheria, measles or scarlet fever, decreases markedly the risk of this complication.

Allergic Encephalomyelitis

Diffuse encephalomyelitis may complicate the administration of horse serum, bacterial vaccines (pertussis and typhoid), toxoids, and virus vaccines (rabies). As a rule, the nervous system manifestations appear about 10 to 12 days after the offending agent is given. The clinical picture may be *very mild and be featured only by slight monoplegia or* mononeuritis On the other hand, involvement of the brain and spinal cord may be so diffuse that dysfunction of all parts of the nervous system appears and death occurs rapidly. This disorder is said to occur most often in individuals who have a history of atopic allergies. Its development is not always related to the appearance of skin rash or other evidence of sensitization. In cases which have followed pertussis and rabies immunization, however, severe reactions have been noted at the site of injection prior to the appearance of the encephalitis. No prophylactic measures are available; caution must be exercised in immunizing patients with a significant allergic background. It must be stressed, nevertheless, that a history of allergy does not contraindicate immunization in any situation in which it is indicated. Although the writer has had no experience with cortisone in this type of disease, the fact that a hypersensitivity reaction may be involved suggests consideration of the use of corticosteroids in severely ill cases.

Benign Myalgic Encephalomyelitis (Epidemic Neuromyesthenia)

Benign myalgic encephalomyelitis is a recently described disease of the nervous system which is probably infectious in origin. It may be confused clinically with poliomyelitis.

from the acute phase of post-measles encephalitis and the appearance of residua. There is no specific prophylaxis or treatment. Although cortisone has been used, its effectiveness still remains to be proved. The administration of large doses of gamma globulin as a therapeutic measure has also been suggested; there is no evidence that it is effective.

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vibratory, light touch, and pain sensation, pleuritic chest pain (usually unilateral), backache, sore throat, insomnia, somnolence, menstrual disturbances, pain on movement of the eyes, and chills. Fever is usually of low degree.

The white blood count in both forms of the disease is normal, as a rule. Examination of the spinal fluid in the cases with myalgia and muscle weakness reveals no increase in the number of cells, although the protein is usually not increased, it has been found to be elevated in some cases.

The most striking characteristic of the paretic cases is their tendency to enter a subacute stage in which they recrudesce over a relatively long period of time. In many instances, after a misleading improvement, all of the manifestations suddenly become aggravated. The exacerbations tend to be associated with physical exertion, exposure to damp or cold weather, and onset of menstruation; they tend to be repetitive. In general, improvement gradually occurs with progress of time. Many patients complain of not feeling well for a long time after they have apparently recovered. There have been no deaths.

There is no specific therapy for benign myalgic encephalomyelitis. Every effort should be made to relieve the muscle pain, which may be intense, by the administration of analgesic agents such as codeine or Demerol.

This disorder has also been called epidemic neuromyesthenia, Iceland Disease, Tallahassee Disease, Coventry Disease, Akureyri Disease, and epidemic vegetative neuritis.

No specific etiologic agent has been incriminated in the pathogenesis of this disease. A very recent study has suggested the possibility that members of the Bethesda-Ballerup group of bacteria (paracolon) may be involved; this remains to be proved.

The incubation period is about 5 to 8 days. Females are affected much more frequently than males, and the disease appears to occur primarily in epidemic form.

Two clinical types of epidemic myalgic encephalomyelitis have been described; (a) one in which manifestations of a non-specific illness, without localizing signs or symptoms, are present, and (b) another in which, following a prodromal period, evidence of meningeal irritation, myalgia, and paresis of varying degree and distribution develops.

The non-paretic form of the disease ("minor illness") appears in about 50 per cent of patients It is characterized by the presence of grippe-like symptoms which include headache, generalized aching, and low-grade fever. These are sometimes present for only 1 to 2 days. If they persist for more than 5 to 6 days, diarrhea, nausea, and vomiting usually become prominent, less frequently, mild respiratory symptoms such as coryza and sore throat develop.

The paretic type of benign myalgic encephalomyelitis is usually preceded for 4 to 6 days by prodromal manifestations which are similar to the syndrome of the "minor illness." As muscle weakness develops, all of the symptoms become more marked. The outstanding features of the paretic form of the disease are stiff neck, stiff back, a peculiar feeling of heaviness and numbness in one or more extremities, muscle tenderness, myalgia which may be very severe, varying degree and distribution of muscle weakness, diarrhea, depression, vasomotor instability (chilliness, pallor, and flushing of the skin), paresthesias, decrease in

by bacteremia), pain, swelling and tenderness are the outstanding manifestations; as the process progresses, fluctuation may become apparent. Peripheral leucocytosis with a significant increase in neutrophiles is the rule. The lesions may be overlooked when they occur as part of a generalized disease. Intragluteal abscesses secondary to injections may lie very deep in the tissue and, although pain and tenderness may be present, not be recognized because fluctuation may not appear until very late or be completely absent; extensive dissection may, however, take place along fascial planes. The local signs of intramuscular hematoma may not change much when infection supervenes; fever and leucocytosis may appear for the first time or, if previously present, become more marked. Not all abscesses which follow injections are infected. Immunizing agents such as alum-precipitated toxoids and pertussis vaccine and some antibiotics may produce sterile abscesses at sites of inoculation; fever and leucocytosis may be present. The lesions may readily be confused with an infectious process and are sometimes treated with antimicrobial agents. They usually disappear in about a week after the injections which produced them are stopped.

Intramuscular abscesses may become complicated by local extension, vascular thrombosis at the site of infection, pulmonary infarction, and bacteremia with metastatic focalization on the endocardium, meninges, lungs, etc. The writer has studied one patient who developed an intragluteal abscess following an injection of procaine penicillin. Fever, severe leucopenia, and a diffuse bronchopneumonia were present; a small non-fluctuant area of tenderness and redness was present in the buttock. Incision, however, revealed a large deep-seated abscess which had spread diffusely through the gluteal muscles. Blood culture taken prior to operation yielded coagulase-positive, hemolytic *Staph. aureus*. Treatment with large doses of chloramphenicol and erythromycin were undertaken but death occurred

CHAPTER XIV

INFECTIONS OF THE MUSCULO-SKELETAL SYSTEM

Infections of Muscles

Intramuscular Abscesses

Intramuscular abscesses are produced by two mechanisms: (1) direct introduction of bacteria during trauma or the injection of various drugs, and (2) focalization in the course of bacteremia which may be very transient or prolonged. Not infrequently minor injury to a muscle may set up a locus of decreased resistance in which organisms may be implanted and grow readily, or a hematoma which is present becomes infected. Regardless of the mechanism involved, most intramuscular abscesses are produced by *Staph. aureus*. During the course of a bacteremia, other organisms may be involved; a good example of this is typhoid fever in which abscesses may develop spontaneously or appear at the site of injection of drugs. The bacteria introduced during accidental or purposeful trauma are variable and include enteric forms such as *E. coli*, *Bacteroides*, *Clostridium welchii*, and other pathogenic anaerobes. A number of intragluteal abscesses due to gram-negative bacteria have followed the intramuscular administration of penicillin.

With the exception of gas gangrene and other anaerobic infections, the clinical picture of intramuscular abscess does not differ in relation to the causative agent. Fever, chills in the severe cases (especially those which are accompanied

dated during the last two World Wars. (2) A vascular injury with resulting ischemia predisposes to gas gangrene. In some cases, the infection does not appear even when the causative agents are present in the tissues unless obstruction to blood flow supervenes and causes necrosis. The application of tourniquets for prolonged periods, failure to relieve tension by splitting of fascia at operation when muscle injury is accompanied by marked edema, and the use of tight plaster casts may be responsible for ischemia and set the stage for gas gangrene in patients with anaerobe-contaminated wounds.

The bacteria responsible for gas gangrene and the milder forms of anaerobic wound infection are *Clostridia*, gram-positive, spore-forming anaerobic rods Although *Cl welchii* (*Cl. perfringens*) is the organism most commonly involved in anaerobic myositis, many infections are due to the simultaneous presence of *Cl. novyi* (*Cl oedematiens*) or *Cl. septicum* (*Vibrion septique*). Non-pathogenic strains such as *Cl. putrificum*, *Cl. sporogenes*, and others are also frequently demonstrable. It has been suggested that these are necessary for the development of true anaerobic myositis.

Three types of infection are produced by the *Clostridia:* (1) simple contamination, (2) anaerobic cellulitis, and (3) anaerobic myositis (gas gangrene).

Clostridia contaminate many wounds All species have been detected; during World War II, 20 to 30 per cent of all wounds were found to contain pathogenic and non-pathogenic anaerobic bacilli. With simple anaerobic contamination, there is no invasion of tissues.

When *Clostridia* multiply rapidly and spread into the connective tissues, they produce large quantities of gas which escape into the spaces and open them, making penetration by the organism easier. Large pockets of gas (gas abscess) are the outstanding finding. This is the picture of anaerobic cellulitis. The incubation period is approximately 3 to 4 days. The onset is more gradual than in anaerobic

in about 18 hours. Autopsy revealed a large, dissecting intragluteal abscess, thrombosis of the blood vessels in the area, multiple pulmonary infarcts, and diffuse staphylococcal bronchopneumonia.

The treatment of infected intramuscular abscesses involves the use of both antimicrobial drugs and surgical drainage. If the lesion is detected early, antibiotic agents may eradicate it. If cultures are not available for sensitivity testing, it is probably best to start with aqueous penicillin (250,000 units intramuscularly every 4 hours) especially if the infection has started outside the hospital. If the lesion arises at the site of injection of an antibiotic, the responsible drug cannot be given because the organisms are obviously not susceptible to it. Intramuscular abscesses which develop in hospitalized patients are frequently due to penicillin-resistant *Staph. aureus*. In such cases, the use of chloramphenicol plus erythromycin (0 5 gm. of each orally every 6 hours) is indicated. Therapy should be continued for 2 weeks. In extensive and especially in fluctuant lesions, incision and drainage should be carried out in addition to antimicrobial therapy. The difficulty of detecting such abscesses, particularly when they are situated in the buttocks, cannot be overemphasized; fluctuation may not appear because the lesion often burrows deeply instead of toward the surface.

GAS GANGRENE

True gas gangrene is a myositis. A number of factors predispose to its appearance. (1) Injuries into which anaerobic bacteria (*Clostridia*) are introduced by contaminated soil, tools, etc. are very important. Such wounds are most frequently incurred on farms and in the street because of the presence in these areas of animal feces which contain pathogenic *Clostridia*. The largest number of cases of gas gangrene is usually observed in wounded soldiers, most of the significant information concerning the disease has been eluci-

dated during the last two World Wars. (2) A vascular injury with resulting ischemia predisposes to gas gangrene. In some cases, the infection does not appear even when the causative agents are present in the tissues unless obstruction to blood flow supervenes and causes necrosis. The application of tourniquets for prolonged periods, failure to relieve tension by splitting of fascia at operation when muscle injury is accompanied by marked edema, and the use of tight plaster casts may be responsible for ischemia and set the stage for gas gangrene in patients with anaerobe-contaminated wounds.

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posed at operation is distinctly abnormal, white in color, and gives the impression of having been boiled.

The diagnosis of anaerobic myositis is readily made on clinical grounds. Demonstration of the typical organisms in discharges from the wound is helpful; not only vegetative but sporulated organisms may be detected in stained smears. Cultures in thioglycollate and chopped meat medium readily yield the *Clostridia*. It must be stressed, however, that their isolation from a site of injury does not necessarily imply the presence of anaerobic myositis since they are also present in cases of "simple contamination." Bacteriologic evidence is, nevertheless, helpful in confirming the clinical impression because organisms other than *Clostridia* may be responsible for tissue damage and gas formation; *Proteus*, *E. coli* and other enteric bacteria are occasionally involved in such infections. Traumatic emphysema, air sucked into tracts produced by penetrating missiles, injection of benzene, and contact with finely powdered magnesium may all be associated with the presence of "gas" in tissues and cause confusion with anaerobic myositis or cellulitis.

Anaerobic infections may be prevented in some instances by proper prophylaxis carried out shortly after injury. Trivalent gas gangrene antitoxin (*Cl. welchii*, *Cl. novyi*, and *Cl. septicum*) has been used but does not appear to be very effective in the absence of other procedures. Most important are adequate cleansing and debridement of wounds. Chemoprophylaxis should be instituted early, the drugs recommended for this purpose are (1) chlortetracycline (Aureomycin), (2) oxytetracycline (Terramycin), (3) chloramphenicol, and (4) penicillin The dose of the first three is 500 mg. orally every 4 to 6 hours. The fourth is given in quantities of 400,000 units of the procaine salt together with 200,000 units of the aqueous preparation every 12 to 24 hours for several days.

The treatment of gas gangrene embraces three ap-

myositis. There are very few systemic disturbances. The wound is dirty, has a foul odor, is not especially painful, and exudes a moderate amount of brown, seropurulent discharge. *Gas extends diffusely* between muscle groups, crackles through the subcutaneous tissues, and bubbles up through the clot and exudate. The muscles appear normal at operation and contain no gas; this is the most important point of differentiation from true gas gangrene. If secondary infection with the beta-hemolytic streptococcus takes place, it may be more difficult to separate the two types of disease.

Anaerobic myositis, or true gas gangrene, may follow anaerobic contamination or cellulitis, or appear as the first manifestation of clostridial infection. The incubation period may be as short as 12 hours, or as long as 6 weeks. The earliest symptoms are a sensation of great heaviness and severe pain in the injured limb. There is local edema. The patient appears very ill, may be delirious or maniacal, and has a moderate fever. Shock may develop within a few hours of the generally abrupt onset. Jaundice is sometimes present terminally. Because of the very rapid hemolysis from the action of the alpha toxin of *Cl. welchii*, the skin may become very red, especially if bacteremia supervenes; the hematocrit falls sharply and the icteric index rises. Death from lower nephron nephrosis (acute tubular necrosis) may occur in such cases.

Examination of the site of injury usually reveals only edema and moderate tenderness early in the course of the disease. Little or no gas is detectable. As the infection progresses, there is a sweet odor, profuse bloody or serosanguinous discharge, and gas in the area of the wound. The quantity of gas, however, is never as large as in anaerobic cellulitis. The skin may be slightly blanched or have a "marbled" appearance. With progression, or in terminal or fulminating cases, a red-yellow, brown, green, or black discoloration occurs, and blebs and bullae appear. Muscle ex-

posed at operation is distinctly abnormal, white in color, and gives the *impression* of having been boiled.

The diagnosis of anaerobic myositis is readily made on clinical grounds. Demonstration of the typical organisms in discharges from the wound is helpful; not only vegetative but sporulated organisms may be detected in stained smears. Cultures in thioglycollate and chopped meat medium readily yield the *Clostridia.* It must be stressed, however, that *their isolation from a site of injury does not necessarily* imply the presence of anaerobic myositis since they are also present in cases of "simple contamination." Bacteriologic evidence is, nevertheless, helpful in confirming the clinical impression because organisms other than *Clostridia* may be responsible for tissue damage and gas formation; *Proteus, E. coli* and other enteric bacteria are occasionally involved *in such infections. Traumatic emphysema,* air sucked into tracts produced by penetrating missiles, injection of benzene, and contact with finely powdered magnesium may all be associated with the presence of "gas" in tissues and cause confusion with anaerobic myositis or cellulitis.

Anaerobic infections may be prevented in some instances by proper prophylaxis carried out shortly after injury. Trivalent gas gangrene antitoxin (*Cl. welchii, Cl. novyi,* and *Cl. septicum*) has been used but does not appear to be very effective in the absence of other procedures. Most important are adequate cleansing and debridement of wounds. Chemoprophylaxis should be instituted early, the drugs recommended for this purpose are (1) chlortetracycline (Aureomycin), (2) oxytetracycline (Terramycin), (3) chloramphenicol, and (4) penicillin. The dose of the first three is 500 mg. orally every 4 to 6 hours. The fourth is given in quantities of 400,000 units of the procaine salt together with 200,000 units of the aqueous preparation every 12 to 24 hours for several days

The treatment of gas gangrene embraces three ap-

proaches: (1) surgical excision, (2) antitoxin, and (3) antimicrobial agents. Surgical debridement of the wound is most important and should include not only all the injured tissue but also a margin of normal tissue, if possible. If the vascular supply is impaired, amputation of the involved extremity is necessary even when antibiotics and antitoxin are given; this is especially true when complete occlusion of arteries has been present for some time. Trivalent or pentavalent gas gangrene antitoxin (*Cl. sordelli* and *Cl. histolyticum* antitoxin in addition to the 3 present in the trivalent mixture) must be administered as soon as the disease is suspected. The dose of the pentavalent preparation is 20,000 units of each of *Cl. welchii* and *Cl septicum*, 3,000 units of *Cl. histolyticum*, and 3,000 units each of *Cl. novyi* and *Cl. sordelli* antibody; one-half should be injected intramuscularly and the other half intravenously, after appropriate skin and eye tests for sensitivity. Although it has been suggested that the administration of antitoxin in half the initial dose be repeated daily for several days, this is probably not helpful. If improvement is not occurring, however, this procedure may be followed. It must be emphasized that once a toxin becomes fixed to tissues (this usually takes place very rapidly), it cannot be neutralized by any quantity of antitoxin. Aqueous penicillin, 1,000,000 units, should be given intramuscularly every 3 hours. Some clinicians prefer the tetracycline compounds on the basis of studies in experimental animals. When these are used, the usual dose is 500 mg. orally every 6 hours; in very sick patients, they are best administered parenterally. The intravenous dose should not exceed 2 gms. per day because of the danger of toxic hepatitis. Chemotherapy should be continued for 12 to 14 days. The survival rate in gas gangrene is inversely related to delay in treatment. The fatality rate is highest in cases in which therapy has not been instituted within a few hours of the appearance of the first symptoms of the disease. The importance of pain in the wound and a sensation of heaviness

in the affected extremity cannot be overemphasized as warning signals of impending gas gangrene. The treatment of anaerobic cellulitis is the same as for anaerobic myositis; surgical relief of tension and establishment of drainage are vital.

TRICHINOSIS

Trichinosis is still a relatively common disease in some parts of the United States. Twenty years ago, its incidence on the East and West coasts of this country, as deduced from examination of diaphragms removed at autopsy, was approximately 20 to 25 per cent. Although the prevalence of the disease is presently decreasing because of changes in methods of feeding swine, it is still frequent in some areas. Rats are not implicated in the spread of *Trichinella*. Pigs, especially those fed on raw garbage or slaughter house offal, are the main source of infection in man. Animals raised on grain or cooked garbage are much less dangerous. That many people have had trichinosis without clinical manifestations *is indicated by the fact that 15 to 20 per cent of normal* individuals develop an immediate skin reaction to Trichinella antigen.

Trichinosis is most frequent in the winter months, the time of the year when the ingestion of pork is highest. In the United States, it is observed most often in Maine, Connecticut, New York and California. It has been very common in many European countries, especially Germany and Italy. In the United States it occurs mostly in Italians and Germans, and only rarely in Jews and Mohammedans whose religions interdict the consumption of pork.

When infested pork is eaten by man, the cysts which surround the parasites are removed by gastric digestion. Unless the *Trichinella* have been present in swine muscles for at least 21 days, they will not cause infection because before this age they are not surrounded by a chitinous covering which protects them against the lethal effect of gastric

juice. If they are older than 3 weeks, they are decysted in the stomach, and pass into the small intestine where they reach adulthood in about 2 days. Copulation takes place, the males die and are passed out in the stool, and the pregnant female burrows into the lacteals of the bowel where the larvae hatch in about 7 days. The larvae then enter the venous circulation and reach the lungs, the peripheral circulation, and various muscles. Migration of larvae from the intestinal lymphatics and penetration of the muscles goes on between the 10th and 14th day after ingestion of the infested meat. Encapsulation and calcification of the organisms within the muscles occurs in about 6 to 8 months. The ocular muscles and the masseters are the ones most commonly parasitized. The tongue, larynx, intercostal muscles, diaphragm, and muscles of the extremities (mainly close to tendons and joints) are also infested.

The average incubation period of trichinosis is 7 to 14 days, although it may be as short as 2 days when the number of larvae ingested is very large or as long as 28 days when it is small. Intestinal manifestations occur in the early stage of the disease in some patients, and consist of abdominal pain, fever, and diarrhea which may be so severe that the stools resemble those of cholera. In milder cases the symptoms are malaise, nausea, distension, anorexia, and mild diarrhea. Intestinal symptoms may be absent.

The second stage of the disease may appear several days to a week or more after the intestinal symptoms and is characterized by five features: (1) fever and other signs of infection, (2) evidence of a varying degree of involvement of voluntary muscles, (3) eye signs, (4) complications indicating involvement of the brain, lungs, and myocardium primarily, and (5) peripheral eosinophilia. Edema of the periorbital tissues, conjunctivae, and face occurs in about 75 per cent of patients, producing a picture which has been referred to as "frog facies." There is a severe conjunctivitis, often with hemorrhage, difficulty in movement of the eyes

suggesting ophthalmoplegia, and protrusion of the globes with inability to close the lids in the severe cases. Retinal hemorrhages, papillitis, and diplopia may be present.

The muscles of the extremities are painful, tender, and may show doughy, non-pitting edema. Trismus, weakness, and painful breathing are noted in severe cases. The small amount of movement associated with normal respiration may cause excruciating discomfort.

Macular, petechial, or urticarial skin eruptions may develop. Herpes simplex or herpes zoster are not uncommon. Furunculosis occurs in some instances; *Trichinella* can be demonstrated in these skin lesions in some cases. Subungual hemorrhages appear in 50 to 75 per cent of patients.

The respiratory, cardiovascular, and nervous systems may be involved in the course of trichinosis. Although the *Trichinella* invade these organs, they never encyst in them. Among the signs of respiratory tract infestation are aphonia or hoarseness resulting from invasion of the larynx, edema of the glottis, and difficulty in swallowing due to swelling of the pharynx and tongue. Lobar, lobular, or diffuse pneumonia due to *Trichinella* develops in 10 per cent of cases. Cough is frequent and may be non-productive or yield sputum which may be purulent or contain blood. Severe pleuritis and pleural effusion are sometimes present. Myocarditis (ECG and clinical changes) and pericarditis with effusion may also be observed. Meningoencephalomyelitis or encephalomyelitis occasionally complicate trichinosis, but there are no characteristic features. The spinal fluid may be entirely normal or contain an increased number of cells and protein; rarely, many eosinophiles are present. The passage of large amounts of myoglobin released by the affected muscles may color the urine dark brown or red. Oliguria is present during the stage of acute inflammatory reaction and edema of the muscles.

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The presence of trichinosis is readily suspected in patients in whom all of the classic manifestations, especially severe eye signs and muscle pain and tenderness, are present. The diagnosis must always be confirmed by specific methods, especially in mild cases. A positive complement fixation reaction appears about 25 days after infection and persists for many years; it is of no value, therefore, in the acute case since it may only indicate disease in the past. Attempts at demonstrating larvae in the blood, cerebrospinal fluid, stool, bile, and purulent exudate from furuncles are usually futile. The skin test for trichinosis is positive in 85 to 100 per cent of acute cases, it has little diagnostic significance because it is also positive in 15 to 20 per cent of normal individuals. If the disease has been present for longer than 12 to 16 days, an "immediate" (20 to 30 minutes) reaction follows the endermal injection of *Trichinella* antigen. Prior to this time, the skin reaction is of the tuberculin type and does not develop until 24 to 48 hours after antigen has been given; this has greater diagnostic importance because it does not occur in normal persons. Muscle biopsy reveals the larvae in 50 per cent of cases. The results may be negative in the presence of trichinosis unless biopsy of the right area is carried out; muscle which lies close to a tendon or capsule is most likely to reveal the organisms. The most

establishing the diagnosis is determination of the titer of precipitin against *Trichinella* in a patient's blood. Serums obtained at the beginning of the disease and about two weeks later must be compared. The test becomes positive within 2 weeks, remains so for 1 to 2 years, and is said to be diagnostic in 100 per cent of cases. Repeated skin testing may be responsible for a false-positive precipitin reaction.

The mortality rate of trichinosis in the United States varies from 4 to 15 per cent. The prognosis is influenced by a number of factors. A short incubation period, severe diarrhea, high fever, tachycardia, severe muscle pain, extensive eye involvement, the presence of cardiac, respiratory, or nervous system complications, and long duration of symptoms and signs worsen the outlook for recovery. There is no specific treatment for trichinosis. However, it has recently been shown that the administration of ACTH or cortisone is very effective in producing rapid and marked amelioration of the symptoms and signs in severe cases. The recommended dose of ACTH gel is 50 mg. intramuscularly daily for a week. Intravenous administration of 25 to 50 mg. over an 8 to 12 hour period daily for a week is also effective. Cortisone also produces good results and has been injected in doses of 100 mg. daily intramuscularly for 2 to 3 days or until clinical manifestations have subsided; the quantity is then reduced by 25 mg. each day until therapy is stopped. At this point the patient should be given 25 to 35 mg. of ACTH daily for 2 to 3 days in order to stimulate adrenal activity which was depressed by the use of the corticosteroid.

Epidemic Myalgia (Epidemic Pleurodynia)

Epidemic myalgia (Bornholm disease, devil's grip, epidemic pleurodynia) occurs in sporadic or epidemic form, appears most commonly in children and young adults, is most frequent in summer, and is due to group B Coxsackie virus.

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purative arthritis has been decreasing in incidence because the diseases which it complicated are now frequently cured before joint involvement takes place and because chemoprophylaxis is effective in many instances in preventing bacterial invasion after penetrating joint injuries. Suppurative arthritis still remains a problem, however, and demands immediate recognition and treatment if destruction of tissue and chronic crippling is to be avoided.

Acute suppurative arthritis may be secondary to (1) the introduction of organisms into the synovia or joint space as a result of injury, (2) spread from osteomyelitis (ends of bones) which perforates the periosteum and allows infection of the intracapsular space, and (3) the deposition of bacteria in the synovial membranes during bacteremia. Although a number of organisms may be responsible for the disease, *Staph. aureus* is the commonest offender. The beta-hemolytic streptococcus, meningococcus, gonococcus, *Brucella, Salmonella typhi, S. choleraesuis*, enteric organisms, *Bacteroides* and even *Clostridia* have been implicated in some cases. The nature of the causative agent depends to some degree on the pathogenesis of the infection.

Physical examination in cases of suppurative arthritis does not allow an etiologic diagnosis because, with few exceptions, the findings are similar and not related to a specific organism. The affected joint is swollen, red, painful, and tender. Movement usually increases the discomfort; the extremity may be held rigidly in order to avoid pain. Fluid is usually detectable in the joint space. In addition to the local signs, general manifestations of infection such as fever, chills, and leucocytosis are very common.

Some of the suppurative arthritides possess a few features worthy of special mention. Streptococcal arthritis is practically always secondary to infection with the same organism elsewhere in the body, usually in the respiratory tract. When the disease is secondary to osteomyelitis, *Staph. aureus* and the beta-hemolytic streptococcus are most often

After an incubation period of 2 to 5 days, the disease often starts with malaise, anorexia, and mild general discomfort for about 24 hours; no prodromal manifestations are present in some cases and the onset is abrupt. The temperature is usually 101° to 103° but may rise to 105°. It may fluctuate widely, symptoms increasing in severity as it rises and becoming milder as it falls. Pain is present on one or both sides of the chest, in the epigastrium, or along the attachments of the diaphragm, and is often intermittent, sharp, and stabbing in character. It may be quite mild. The discomfort is aggravated by breathing, coughing, and sneezing. The muscles of the extremities, shoulders, and neck are painful and tender in some instances. Headache may be severe. Sore throat, chilliness, vomiting, and photophobia may be present. In many patients, fever and pain decrease in 24 to 48 hours only to recur after one or more days, this feature is observed in 25 per cent of sporadic and 60 per cent of epidemic cases. "Aseptic" meningitis (Chapter XIII) is a rare complication.

Physical examination reveals splinting of the chest and shallow respiration, reddened pharynx, and, in some patients, tenderness to palpation of the muscles of the extremities and neck. The white blood count is elevated or at leucopenic levels.

The course of epidemic myalgia is benign and all cases recover. Defervescence usually takes place in 3 to 5 days although it may require as long as 10 days. Pain may persist for several weeks, however. There is no specific treatment. The liberal use of analgesics for relief of discomfort is recommended.

Infections of Joints

Suppurative Arthritis

A variety of etiologic factors may be responsible for acute and chronic arthritis. One of these is bacterial infection. Since the advent of effective antimicrobial therapy, sup-

forme (Stevens-Johnson syndrome), scleroderma, psoriasis, Reiter's syndrome, and porphyria.

The joint fluid in suppurative arthritis is usually purulent and contains a large number of cells, the majority of which are polymorphonuclear leucocytes; the same finding may, however, be present in some of the non-infectious arthritides. Most helpful in differentiating these types of arthritis are (1) demonstration of bacteria by stained smear and appropriate culture, and (2) detection of a decreased sugar content in the joint fluid when compared to a simultaneously drawn blood sugar; both of these are consistent with bacterial infection. Blood cultures should be carried out in every case; in some instances, the causative organisms may be recovered from the blood earlier and with greater ease than from the exudate in the joint space.

Untreated suppurative arthritis most often progresses to *destruction of the joint surfaces and results in crippling due* to fibrosing and later bony ankylosis. Metastatic infections in other tissues may result from invasion of the blood stream. Because failure to treat effectively may lead to serious sequelae and residua, it is imperative that the etiologic diagnosis be established *as rapidly as possible* and *specific therapy initiated promptly*. The type of antimicrobial agent used depends on the nature of the bacteria causing the disease. For most staphylococcal and all beta-hemolytic streptococcal infections, aqueous penicillin is the agent of choice. It should be given in a dose of 500,000 units intramuscularly every 4 hours for at least 2 weeks. All strains of staphylococci isolated from joint fluids must be examined for sensitivity to various antibiotics so that the most effective drug may be used. Some clinicians favor local treatment in addition to the systemic administration of the antimicrobial agent, and inject *100,000 to 200,000* units of aqueous penicillin directly into the infected joint space every 12 to 24 hours (3 or 4 doses) in cases of staphylococcal (penicillin-sensitive) or streptococcal infection. Bacitracin, neomycin, polymyxin, and erythromycin may be given in the same

involved because they produce infection of bone very commonly. However, the typhoid bacillus, *Salmonella choleraesuis*, and other bacteria may also cause osteomyelitis and complicating joint involvement. Arthritis often occurs in the course of rat-bite fever (Chapter XVI). Suppurative arthritis develops in meningococcal infections, usually at the height of the disease. The organisms can be cultured from the exudate in the joint space; a sterile effusion is present during convalescence in some cases.

Arthritis is present in about 0.1 to 0.3 per cent of patients with untreated gonorrhea. About one-quarter of the cases are due to direct invasion by the organism as demonstrated by positive cultures of joint fluid. In the others, the fluid is sterile; it has been suggested that this type is due to an immune reaction. The joint involvement usually occurs in from 1 to 3 weeks after the primary disease, but its appearance may be delayed for as long as many months or even years. Polyarthritis is frequent, larger joints being affected most often; monoarthritis is also common. Tenosynovitis is present in many cases. (Chap. XII)

Although monoarticular involvement is most common with bacterial infection, polyarthritis which may be migratory in character is frequently observed in the course of some situations. This is the case in meningococcal, gonococcal, *Streptobacillus moniloformis*, *Brucella*, *Salmonella*, and even staphylococcal and streptococcal arthritis. In such cases, the clinical differential diagnosis is often very difficult or impossible because migrating polyarthritis may also be present in a number of non-bacterial and even non-infectious disorders. These include lymphogranuloma venereum, mumps, infectious mononucleosis, rubella, syphilis, hemophilia, sickle cell anemia, Henoch-Schoenlein purpura, serum sickness, polyarteritis nodosa, trichinosis, coccidiomycosis, lymphoma, carcinoma of the lung, rheumatic fever, disseminated lupus erythematosus, rheumatoid arthritis, gout, uremia, ulcerative colitis, exudative eryth[illegible]ulti-

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fashion. This procedure is thought to speed elimination of the causative bacteria, reduce the degree of damage, and hasten recovery. When organisms other than staphylococci or beta-hemolytic streptococci are involved, the antimicrobial agents to which they are most susceptible must be administered; the minimum period of therapy is 2 weeks.

OSTEOMYELITIS

Acute osteomyelitis occurs primarily during childhood and adolescence, the commonest age being 8 to 16 years. Bacterial invasion of bone takes place by one of three routes: (1) spread from an infectious process in the surrounding soft tissues, (2) direct introduction in compound fractures, and (3) hematogenous implantation during the course of bacteremia (*transient or prolonged*). In the neonatal period the disease may follow infection of a cephalhematoma or the umbilical cord, or pustular dermatitis; it may result from injury to the rich venous plexus in the jaw incident to suckling. Skin infections are one of the most important factors predisposing to the development of acute osteomyelitis. Other conditions which set the stage for the disease are respiratory tract infections, extraction of teeth, pneumonia, empyema, bronchiectasis, cholecystitis, enterocolitis, liver abscesses, subacute bacterial endocarditis, decubitus ulcers, chronic ulcerations of the extremities, infected open wounds, and carbuncles. A history of trauma is obtained in two-thirds of the cases; this is the most important predisposing factor and may be limited to the soft tissues.

Staphylococcus aureus is the organism responsible for acute osteomyelitis in 90 per cent of cases About 3 to 5 per cent are due to the beta-hemolytic streptococcus, the typhoid bacillus is responsible for about 0 8 per cent. Other bacteria which may be involved occasionally include the pneumococcus, gonococcus, *H. influenzae*, and *Salmonellae*.

The femur is the bone most frequently affected, the lower

third is the most susceptible area. Next in order of frequency are the tibia (upper third), humerus (upper third), fibula (lower third), radius (lower third), and calcaneus. Among the other bones which may be involved are the ulna (lower third), skull, mandible, clavicle, sacrum, metatarsals, vertebrae, scapulae, pelvic bones, metacarpals, sternum, and ribs (most frequently typhoid bacillus). Only one bone is usually affected, but two or more are involved in some cases.

In instances in which trauma is the predisposing factor, the incubation period of osteomyelitis is 2 to 7 days. A prodromal phase precedes the development of signs of bone disease for 1 to 4 days and is characterized by fever, leucocytosis, anorexia, apathy, and malaise; chills may be present. The most important symptom of the disease is rapidly increasing pain. The outstanding sign is marked "point" tenderness over the area of infected bone. In the full-blown picture, the patient appears severely ill, has a high fever, suffers repeated chills, complains bitterly of localized boring pain, shrieks with the discomfort produced by pressure over the affected area, and is unable to move the joint close to the involved portion of the bone. The extremity below the lesion is edematous. Deep fluctuation is slow to develop and usually does not appear unless the periosteum is involved, or perforation of the cortex leads to the development of subperiosteal abscess. The regional lymph nodes are enlarged and tender. Bacteremia is common in severe cases. High grade leucocytosis is the rule, although leukopenia with granulopenia may appear in fulminating cases in which bacteremia due to *Staph. aureus* is often present. X-ray examination usually does not reveal destruction of bone until 7 to 12 days after the disease starts.

If the patient survives the acute phase of the infection, necrosis of bone progresses, sequestration takes place, and involucrum forms. The area of destruction may be very extensive and involve the entire shaft; this is not due entirely to infection but results, in good part, from thrombosis

fashion. This procedure is thought to speed elimination of the causative bacteria, reduce the degree of damage, and hasten recovery. When organisms other than staphylococci or beta-hemolytic streptococci are involved, the antimicrobial agents to which they are most susceptible must be administered; the minimum period of therapy is 2 weeks.

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The femur is the bone most frequently affected; the lower

third is the most susceptible area. Next in order of frequency are the tibia (upper third), humerus (upper third), fibula (lower third), radius (lower third), and calcaneus. Among the other bones which may be involved are the ulna (lower third), skull, mandible, clavicle, sacrum, metatarsals, vertebrae, scapulae, pelvic bones, metacarpals, sternum, and ribs (most frequently typhoid bacillus). Only one bone is usually affected, but two or more are involved in some cases.

In instances in which trauma is the predisposing factor, the incubation period of osteomyelitis is 2 to 7 days. A prodromal phase precedes the development of signs of bone disease for 1 to 4 days and is characterized by fever, leucocytosis, anorexia, apathy, and malaise; chills may be present. The most important symptom of the disease is rapidly increasing pain. The outstanding sign is marked "point" tenderness over the area of infected bone. In the full-blown picture, the patient appears severely ill, has a high fever, suffers repeated chills, complains bitterly of localized boring pain, shrieks with the discomfort produced by pressure over the affected area, and is unable to move the joint close to the involved portion of the bone. The extremity below the lesion is edematous. Deep fluctuation is slow to develop and usually does not appear unless the periosteum is involved, or perforation of the cortex leads to the development of subperiosteal abscess. The regional lymph nodes are enlarged and tender. Bacteremia is common in severe cases. High grade leucocytosis is the rule, although leukopenia with granulopenia may appear in fulminating cases in which bacteremia due to *Staph. aureus* is often present. X-ray examination usually does not reveal destruction of bone until 7 to 12 days after the disease starts

If the patient survives the acute phase of the infection, necrosis of bone progresses, sequestration takes place, and involucrum forms. The area of destruction may be very extensive and involve the entire shaft; this is not due entirely to infection but results, in good part, from thrombosis

fashion. This procedure is thought to speed elimination of the causative bacteria, reduce the degree of damage, and hasten recovery. When organisms other than staphylococci or beta-hemolytic streptococci are involved, the antimicrobial agents to which they are most susceptible must be administered; the minimum period of therapy is 2 weeks.

OSTEOMYELITIS

Acute osteomyelitis occurs primarily during childhood and adolescence, the commonest age being 8 to 16 years. Bacterial invasion of bone takes place by one of three routes: (1) spread from an infectious process in the surrounding soft tissues, (2) direct introduction in compound fractures, and (3) hematogenous implantation during the course of bacteremia (transient or prolonged). In the neonatal period the disease may follow infection of a cephalhematoma or the umbilical cord, or pustular dermatitis; it may result from injury to the rich venous plexus in the jaw incident to suckling. Skin infections are one of the most important factors predisposing to the development of acute osteomyelitis. Other conditions which set the stage for the disease are respiratory tract infections, extraction of teeth, pneumonia, empyema, bronchiectasis, cholecystitis, enterocolitis, liver abscesses, subacute bacterial endocarditis, decubitus ulcers, chronic ulcerations of the extremities, infected open wounds, and carbuncles. A history of trauma is obtained in two-thirds of the cases; this is the most important predisposing factor and may be limited to the soft tissues.

Staphylococcus aureus is the organism responsible for acute osteomyelitis in 90 per cent of cases About 3 to 5 per cent are due to the beta-hemolytic streptococcus; the typhoid bacillus is responsible for about 0 8 per cent Other bacteria which may be involved occasionally include the pneumococcus, gonococcus, *H. influenzae*, and *Salmonellae*.

The femur is the bone most frequently affected; the lower

Untreated acute osteomyelitis may undergo spontaneous resolution in a small number of cases. The acute inflammation of the bone may progress to suppuration without necrosis. In the majority of cases, destruction and sequestration occur. The fatality rate varies from about 2 to 25 per cent and is higher in males than females. The prognosis is made worse when the following features are present: (1) age at which greatest activity of bone growth is present, (2) infection due to *Staph. aureus*, (3) severe clinical manifestations, (4) high grade bacteremia, (5) involvement of the skull, spine, and jaws, in this order, (6) appearance of complications, such as meningitis, myelitis, cerebral or pulmonary embolism, lung abscess, acute endocarditis, and renal disease, (7) cutaneous hemorrhages in the first few days of the disease, and (8) development of icterus. About two-thirds of the deaths occur within the first 10 days.

Specific therapy must often be initiated in acute osteomyelitis before roentgenographic evidence appears. All patients should be hospitalized. Since most cases are due to *Staph. aureus*, it is best to start treatment with 500,000 to 1,000,000 units of aqueous penicillin given intramuscularly every 4 hours. If the infection is due to a penicillin-resistant organism, as suggested by lack of improvement after 2 to 3 days of therapy, it is probably best to change to 0.5 gm. of chloramphenicol plus 0.5 gm. of erythromycin every 6 hours. Because infections of bone are always relatively difficult to eradicate even with highly potent antimicrobial drugs, treatment should be continued for a minimum of 3 to 4 weeks. Surgical therapy is not indicated unless subperiosteal or soft tissue abscess is present; in these cases, it should be limited to drainage. With early and intensive administration of potent antimicrobial agents, the outlook for complete recovery with minimal bone necrosis and without the development of complications or chronicity is excellent. In chronic osteomyelitis, chemotherapy alone will not cure the disease. Removal of necrotic bone, plus the use of antibiotic agents to which

of the nutrient arteries which is present in practically every case. Without antimicrobial therapy, death may occur in the acute stage of the disease, especially if staphylococcal bacteremia occurs. Chronicity may develop; this is characterized by draining skin sinuses which may close periodically only to reopen sometime later. Low grade activity, interspersed with periods of clinical quiescence, may continue for many years.

Acute suppurative arthritis is the most common complication of osteomyelitis and results from direct extension of infection into the joint space. This develops in adults as the disk of cartilage between the shaft and epiphysis disappears. The joints most often affected in children are those in which the synovial lining is reflected on the metaphysis beyond its junction with the epiphysis or in which the articular cartilage is continuous with the metaphysis, as at the upper end of the ulna. Tenosynovitis may arise by direct extension and occurs most frequently in the fingers. Pathologic fracture may take place; it is commonest in the metaphysis but may also occur at the line of sequestration. Meningitis or brain abscess may complicate osteomyelitis of the skull; myelitis, meningitis, mediastinitis, pericarditis, or empyema may follow involvement of the spine, ribs or sternum Metastatic foci of infection in other bones or organs result from uncontrolled bacteremia. In patients with chronic osteomyelitis cross union, hypertrichosis of the skin over the affected area, overgrowth or arrest in bone growth, and amyloidosis with renal failure may be observed.

The diagnosis of acute osteomyelitis is suspected on the basis of the signs and symptoms described above. Most important points are a history of trauma, the presence of some type of skin infection, constitutional reaction, pain, and "point tenderness" in the involved bone. X-ray is helpful only after 7 to 12 days. Blood cultures should always be obtained.

CHAPTER XV

INFECTIONS OF THE SKIN

Suppurative Lesions of the Skin

The most common infections of the skin are the pustular dermatitides. These are of 3 main types: furunculosis, carbuncle, and impetigo. All are produced by *Staph. aureus,* although impetigo in very young infants may be due to the beta-hemolytic streptococcus (pemphigus neonatorum). Furuncles and carbuncles are infections of the hair follicles and differ only in that the latter are most extensive and involve more than one follicle.

Impetigo and furunculosis are relatively minor problems from the standpoint of discomfort and risk, if they are not complicated by local or systemic extension. As a rule, the signs and symptoms (swelling, redness, and pain) are limited to the area in which the lesions are located. Systemic response is minimal or absent unless the infection is severe or complications occur. Carbuncles produce more marked manifestations and are often accompanied by considerable pain, malaise, fever, and limitation of movement, particularly if they are present on the neck, a site on which they commonly appear. In the early stages, impetigo may be easily confused with other skin disorders; the initial lesion is a small vesicle surrounded by a thin areola of inflammatory reaction and resembles chicken pox. As the disease progresses, the vesicles rupture and are covered by a soft, golden yellow crust composed of staphylococci and fibrin; this stage is easily distinguishable from the late lesion of varicella, the covering of which is dark brown and hard.

the organisms present in the exudate are susceptible, will produce eradication of the disease in most cases.

Special Forms of Osteomyelitis

Acute Epiphysitis: The focus of infection is present in the epiphysis. Otherwise, this disease does not differ from acute osteomyelitis.

Acute Bone Abscess: This develops in the course of osteomyelitis and is due to an accumulation of purulent exudate within the cancellous mesh, medullary cavity, or endosteum. The margins of the lesion are ill-defined and there is no definite capsule. Acute bone abscesses are relatively common in acute osteomyelitis, progress rapidly, and may be present at any site in the shaft of a bone. They frequently perforate the cortex and produce a subperiosteal abscess. Spontaneous healing occurs frequently; if it does not take place or surgical treatment is employed, the lesion may become chronic.

Chronic Bone Abscess (Brodie's Abscess): This is always situated in the metaphyses of a long bone and lies within the cancellous mesh and not in the medullary cavity. Practically all cases are due to *Staph. aureus,* but some are produced by *S. typhi* or *E. coli.* Three stages have been described: (1) quiescent, (2) mature abscess, and (3) rupture. The mature abscess is characterized by localized pain and tenderness over the involved area; the discomfort is greatest at night. The lesion may be present for as long as 10 to 20 years without producing symptoms. Fever is usually absent until the mature stage is present or rupture into the subperiosteal area occurs. Complications and bacteremia are not observed.

The diagnosis of these special forms of osteomyelitis is established by x-ray study. Treatment for acute epiphysitis and acute bone abscess is the same as for acute osteomyelitis, while that of chronic bone abscess is the same as for chronic osteomyelitis.

given to patients with large carbuncles or infected eczema, especially if fever and other manifestations of infection are present. Aqueous penicillin (200,000 units intramuscularly every 4 hours) is indicated in hospitalized cases; in ambulatory ones, 600,000 units of procaine penicillin once daily may be used. Treatment should be continued for 10 to 12 days. The causative organisms must be isolated and tested for sensitivity to various antibiotics. If penicillin is not producing a satisfactory response, the drug to which the bacteria have been shown to be most susceptible must be administered.

All furuncles do not require incision and drainage. This operation is indicated when the lesions are large, painful, *fluctuant*, and show no tendency to empty spontaneously; care must be taken to limit the incision to the necrotic area because of the danger of dissemination of the organisms which may become a problem if the surrounding zone of protective inflammatory reaction is disturbed. Carbuncles usually require surgical treatment. Squeezing of suppurating lesions of the skin is extremely dangerous and often results in spread of infection and bacteremia.

The complications of suppurative skin lesions usually are secondary to invasion of the blood stream by the organisms and include acute endocarditis, multiple pulmonary abscesses, brain abscess, venous sinus thrombosis, purulent meningitis, acute pericarditis, and suppurative renal disease.

Acute Cellulitis

Acute cellulitis is an acute inflammatory reaction in the skin and subcutaneous tissues; it is characterized by a *tendency* to spread. The beta-hemolytic streptococcus and *Staph. aureus* are most frequently the causative agents, but other bacteria may also be responsible. *Clostridia* produce "anaerobic cellulitis" (Chapter XIV). Fever of varying degree, generalized malaise, shaking chills, and headache may be

Superimposed staphylococcal or beta-hemolytic streptococcal infection may occur in areas of eczema. In a study in a large hospital, it was found that this was a very common predisposing factor to the development of acute diffuse glomerulonephritis.

Furuncles and carbuncles may be recurrent over a period of years in some individuals. In most cases, the lesions remain limited to the skin; in others, however, they may extend to the deeper tissues or be responsible for bacteremia. Patients with recurrent "boils" must be studied for diabetes mellitus; a glucose tolerance test should be carried out if fasting blood sugar and urine examination are normal. Acquired agammaglobulinemia or hypogammaglobulinemia may also be responsible for repeated or continuing furunculosis; the diagnosis is established by electrophoretic study of the serum. In some cases, the possibility of autoinoculation, exposure to materials such as oils, cutting compounds, etc. which may be contaminated with staphylococci, contact with individuals who have furunculosis, dermatitis factitia, and poor personal hygiene must be considered. In many instances, the mechanism of recurrent furunculosis is never detected.

The diagnosis of suppurative lesions of the skin is usually made entirely on the basis of their appearance. Bacteriologic studies are not necessary unless a complication develops. Simple furunculosis does not require the use of antimicrobial agents either locally or systemically. The application of moist heat to the infected areas relieves discomfort and hastens rupture or resolution. Although bacitracin, neomycin, and other antibiotic ointments have been recommended for the treatment of impetigo, there is no critically evaluated evidence that they are helpful; sensitization to these drugs is most frequent when they are applied locally. Thorough scrubbing of the lesions to remove the crusted exudate and, in some instances, the use of mercury ointment are all that is required to cure most cases. Antibacterial agents should be

Acute Lymphangitis

Lymphangitis is an acute inflammation of the deep or superficial lymphatic channels which is most often due to invasion by beta-hemolytic streptococci or *Staph. aureus*. Two types of the disease are recognized: (1) reticular or capillary lymphangitis which involves the lymphatic vessels in any area of the skin, and (2) tubular lymphangitis which occurs mainly in the extremities.

Manifestations of infection—fever (102-105°), malaise, shaking chills, generalized aching, and headache—are frequently present. In reticular lymphangitis, there is local tenderness, pain, and redness of the involved area, usually an infected site in the skin. In 1 to 2 days, red, linear streaks leading from the local lesion to the regional lymph nodes appear and are accompanied by patchy areas of inflammation. Tubular lymphangitis usually follows a wound of the hand, an infected blister of the foot, or an infected ingrown toenail. The general signs and symptoms of infection are present, but vary in degree in relation to the severity of the lymphangitis. Irregular, painful red streaks extend from the local lesion in the extremity to the regional lymph nodes. The white blood count is elevated (15,000 to 30,000 per mm^3) with a marked increase in neutrophiles.

The complications of lymphangitis are necrosis, necrotizing ulcers, cellulitis with suppuration, and bacteremia with metastatic infection of various organs. The nature of the causative organism, the presence of complications, the general physical condition of the patient, and age influence the prognosis.

The diagnosis of acute lymphangitis is made on the basis of the physical findings described above. Therapy is the same as for cellulitis. Surgical treatment must be avoided because of the danger of bacteremia.

present, their intensity varying with the severity of the disease. In addition, the site of infection is red, swollen, painful, tender, warm, and the borders are poorly defined; fluctuation may develop. Acute lymphangitis and regional lymphadenitis are common. The complications of cellulitis are bacteremia, abscess formation, acute lymphangitis and lymphadenitis, and loss of skin over the affected area. In some cases, the nature of the complication is determined by the location of the infection; thus, in cellulitis of the scalp, spread of the disease through the pericranium and emissary and diploic veins may result in intracranial disease.

Cellulitis is potentially a serious disease. The prognosis is least favorable in very young children and in adults over the age of 40 years. In general, the outlook for uncomplicated recovery is better when infection is produced by the beta-hemolytic streptococcus than when it is due to *Staph. aureus*, strains of which are often antibiotic resistant.

The diagnosis of cellulitis is establishd by physical examination. When the disease involves the face or trunk, it may be mistaken for erysipelas. The main point of differentiation is the appearance of the edge of the lesion; in cellulitis it is indistinct and blends into the normal tissue, whereas in erysipelas the margin is very sharply defined and clearly separated from the uninvolved area.

All cases of cellulitis must be treated with antimicrobial agents. Since most of them are caused by staphylococci or streptococci, initial therapy should consist of aqueous penicillin (250,000 units intramuscularly every 6 hours). For patients at home, a daily injection of 1,200,000 units of procaine penicillin may suffice in some instances; this is not always effective. If the response is poor, it is best to administer chloramphenicol *plus erythromycin (0.5 gm. of each orally* every 6 hours) because of the possibility that a penicillin-resistant strain of *Staph. aureus* is involved. Sensitivity tests of recovered organisms should be carried out whenever possible.

by recovery in many instances. However, there is a marked tendency to relapse; this may occur a number of times, involve the same area of skin, and be followed by chronic lymphatic obstruction and a varying degree of elephantiasis.

The diagnosis of erysipelas is established on the basis of the appearance and course of the lesion. Bacteriologic study is usually of little help. Group A beta-hemolytic streptococci may be isolated from the nose or throat in some cases. The organisms usually cannot be recovered from the surface of the involved skin; they may be demonstrable by culture of tissue fluid obtained from the advancing edge of the lesion by needle puncture.

The therapy of choice for erysipelas is penicillin. A dose of 600,000 units of the procaine preparation daily for 7 to 10 days cures the disease rapidly and prevents complications. In *patients sensitive to penicillin, erythromycin* (0.25 gm. orally every 6 hours) may be substituted. Relapse is rare in adequately treated cases.

Streptococcal Gangrene

Beta-hemolytic streptococcal gangrene may develop in any area of the skin, but involves the extremities most often. The disease usually begins in a superficial wound, at the site of a needle puncture, or in a "pimple" or furuncle; occasionally no preceding lesion can be detected. The affected limb is red, hot, swollen, painful, heavy, and quite useless, later, it may become numb. The periphery of the lesion is red and edematous but not raised or sharply demarcated. Fever and apathy are common. Chills are infrequent. An alarming degree of spread may occur in the first 24 to 72 hours. The affected area begins to assume a dusky hue about the second to fourth day. Vesicles and large bullae appear and discharge a dark-colored fluid when they rupture. As the disease progresses, the lesion tends to spread in all directions. In untreated cases, it becomes black or gray

Erysipelas

Erysipelas is an acute lymphangitis of the skin due to the beta-hemolytic streptococcus (*Strep. pyogenes*). It occurs most commonly in very young children and people over the age of 50, although it may be observed at any age. The source of the organisms is usually the upper respiratory tract, most frequently the nose; cultures from these areas frequently do not reveal the streptococci, however. The disease starts in a small break in the skin, although this is not detectable in the majority of cases.

Erysipelas begins as a small area of redness which gradually enlarges. Characteristically, the center of the lesion becomes pale as it spreads; the periphery is bright red, with tongues of inflammatory reaction extending from the advancing edge which is elevated by edema and sharply demarcated from the normal skin. The involved area is hard and indurated. Vesicles and large bullae filled with clear fluid are present in severe cases. The "flush" area of the face is affected in about 75 per cent of patients. The lesion in this site is practically always bilateral and has a "butterfly" appearance. Pain develops as the disease progresses but is not present before it starts. These two features distinguish erysipelas from early herpes zoster of the maxillary portion of the 5th cranial nerve (elsewhere in this chapter). Any area of the skin may be involved. In very young babies, the lesion may be secondary to infection of the umbilical stump and appear on the anterior abdominal wall.

Uncomplicated erysipelas remains confined to the lymphatic vessels. In some instances, however, the streptococci break through the lymphatics and produce cellulitis and subcutaneous abscesses; this may be followed by bacteremia and metastatic infection of various organs. If superinfection by *Staph. aureus* occurs, hemorrhagic vesicles appear and gangrene may supervene. The untreated disease is followed

between muscle bundles and erode vascular channels, causing death from hemorrhage.

The diagnosis of chronic undermining ulcer is made on the basis of the appearance of the individual lesions and the chronic, progressive course of the disease. It is confirmed by isolation of microaerophilic streptococci from beneath the undermined edge of the ulcers. Treatment is both surgical and medical. Necrotic tissue should be removed, drainage established where necessary, and skin grafting carried out to replace lost tissue. The choice of chemotherapy depends on the sensitivity of the offending strain of streptococci to various antibiotic agents The drug to which the organisms are most susceptible should be administered for at least 2 weeks. Local application of activated zinc peroxide or bacitracin has been recommended.

Synergistic Gangrene

Synergistic gangrene of the skin results from simultaneous infection by a microaerophilic streptococcus and *Staph. aureus;* the latter may rarely be replaced by *Proteus*. The streptococci are present in the spreading edge and the staphylococci in the gangrenous area of the lesion. The disease may begin at the site of operative wounds following drainage of a peritoneal abscess or empyema, around a colostomy or ileostomy opening, or in a trivial wound.

Infection usually starts during the first or second postoperative week. The wound becomes red, swollen, and tender. The periphery of the lesion is red; the center becomes purple at first and then gangrenous. As the skin is lost, a shaggy ulcer appears; the skin surrounding it is gray-brown in color and resembles suede leather. Destruction of skin is not always complete; islands of epithelium regenerate from the hair follicles and sweat glands.

The treatment of progressive bacterial synergistic gangrene may be very difficult. Penicillin in large doses cures

in color as gangrene develops. New sites of involvement appear as the process continues to advance. The gangrenous skin begins to separate about the eighth to tenth day disclosing widespread necrosis of the subcutaneous tissues. *Phlebitis* is common, but lymphangitis and lymphadenitis are rare. In some instances, the disease terminates spontaneously with recovery; in most, however, the infection progresses, blood cultures become positive, and metastatic abscesses appear in the lungs or at pressure points in the subcutaneous tissue if antimicrobial therapy is not instituted.

The early recognition and intensive treatment of streptococcal gangrene is imperative. Patients must be hospitalized *and given 1,000,000* units of aqueous penicillin intramuscularly every 4 to 6 hours for 12 to 14 days. This produces rapid cessation of activity and advance of the lesion in most instances and, if given early, decreases the intensity of gangrenous changes and loss of skin. The outlook for recovery is poor in individuals over the age of 50 in whom the disease is severe and treatment has been delayed. There may be considerable loss of skin requiring extensive grafting in those who survive.

Streptococcal Burrowing Ulcer of the Skin

Streptococcal burrowing ulcer is an uncommon disease. It is due to a microaerophilic streptococcus and is characterized by undermined ulcerations which burrow beneath normal skin on the trunk and extremities. The infection may start in operative wounds, accidental injuries, furuncles, or chronic ulcers secondary to burns or trauma. As the undermined skin is eroded from below, new perforations appear and bridges of normal tissue are left between the primary and secondary openings. The ulcers gradually merge to involve large areas. Continual pain, fever, and progressive loss of weight are the usual manifestations. Although the process does not penetrate muscle, it may extend

pustule. This appears most frequently on the skin of the arms, and, in order of decreasing frequency, on the face, neck, head, hand, abdomen, trunk, lower extremities, and shoulders. The initial lesion is a small red, raised papule which is often mistaken for a "pimple" or bite. Shortly after it develops, it becomes surrounded by an area of edema on which are superimposed numerous small vesicles filled with clear fluid. Necrosis of the center of the papule occurs gradually and the area is covered by a black eschar. As the disease progresses, the eschar becomes larger and the ring of surrounding edema increases in size and spreads. Marked swelling may extend for some distance from the lesion. Lymphangitis and regional lymphadenopathy are very common. Although the malignant pustule is usually single, multiple lesions are occasionally observed. As healing takes place, the eschar separates and the edema gradually subsides. Bacteremia occurs occasionally. Although associated with a high death rate, the mere presence of the organisms in the blood does not always constitute an unfavorable prognosis.

Systemic manifestations of varying severity occur in patients with anthrax (malignant pustule). Headache, fever, malaise, generalized muscle pains, and nausea may be present in some cases. In others, there are no symptoms or signs other than those associated with the local lesion. When the disease is severe, vomiting, peripheral vascular collapse, cyanosis, profuse sweating, and hypothermia are frequently observed. The temperature is moderately elevated in most instances, but it may be normal. There is usually some degree of leucocytosis and increase in the number of neutrophiles; leukopenia may also be present.

Invasion of the blood stream by the organisms is the most serious complication of anthrax. Laryngeal edema may appear when the lesion is situated in or near the anterior cervical triangle. If it is located below the jaw or in the periorbital area, gangrene may occur. Contractures may

some cases; the organisms may be resistant to this agent, however. Bacitracin (20,000 units intramuscularly every 6 hours) and chloramphenicol (0.5 gm. orally every 6 hours) may be effective in some instances. The final choice of antimicrobial drug must be made on the basis of tests of sensitivity of the responsible organisms to various antibiotics. It has been suggested that surgical extirpation of the lesion plus the local application of activated zinc peroxide may be successful when other methods of therapy have failed.

Anthrax

Anthrax is primarily an infection of animals; it is secondarily transmitted to man. The disease is widespread and occurs in nearly every country of the world. It affects primarily cattle, sheep, pigs, horses, and goats, but may also appear in dogs, cats, camels, buffaloes, elephants, deer, and even in beasts of prey. Man becomes infected by handling animals or their products which harbor *Bacillus anthracis*. Farmers, butchers, veterinarians, upholsterers, sheep herders, wool, hair, tannery and rug workers and those who make leather gloves, shoes and harness are most frequently susceptible. Anthrax has also followed insect bites, and the use of shaving and tooth brushes made from infected animal bristles.

The causative agent, *Bacillus anthracis*, is a gram-positive, sporulating rod, with square ends. It is the largest bacterium which infects man. Lack of motility, slow fermentation of gelatine, and pathogenicity for animals distinguish it from many other organisms which have a similar appearance ("*Subtilis* group"), but do not produce human disease. Sporulation does not occur *in vivo*. The spores may live in soil for 15 to 20 years. They are not killed by exposure for as long as 5 days to 1:1,000 bichloride of mercury solution or 5 per cent phenol or by the tanning process.

The commonest lesion of anthrax in man is the malignant

of the disease. Treatment should be continued for 10 to 14 days.

Herpes Simplex

Herpes simplex is a very common disease. Practically all persons come in contact with the responsible virus in childhood, live in symbiosis with it for the rest of their lives and, under certain conditions, manifest clinical evidence of its presence. In most instances, the first exposure to the virus produces no clinical manifestations. In some cases (mostly young infants), however, it may result in the development of a severe stomatopharyngitis with high fever, chills, prostration, and multiple painful vesicular lesions which rapidly ulcerate in the mouth and throat.

Once infection with the virus of herpes simplex has taken place, the agent persists in the tissues for many years and probably for life. As long as the host remains well, this symbiotic relationship is preserved. However, when it is disrupted by a special situation (trauma, sunburn, pneumococcal or meningococcal infection, the "common cold", fever from any cause), the virus may gain the upper hand. Since its long residence in the patient has stimulated and maintained antibody against it, the disease which develops tends to be localized and mild. For this reason, the commonest lesion of herpes simplex is the "fever blister" or "cold sore".

The lesions of the localized form of herpes simplex appear first as a group of red papules which lie close to each other, *are surrounded by edema, and produce a burning sensation.* They are quickly transformed into vesicles ("fever blisters") which become umbilicated, rupture, and are covered with a dark crusted eschar within a few days after they first develop. The lesions are most common at the mucocutaneous borders of the mouth but may also be present at other sites. Fever and constitutional reaction are absent. When the penis is involved, the glans or corona is the site of clusters of vesicles. Infection in this area is frequently accompanied by fever;

follow healing of pustules in the vicinity of joints or the eyes. Purulent meningitis may supervene; *the spinal fluid is usually* bloody. Fifty per cent of patients develop cerebral hemorrhages.

The characteristic appearance and development of the malignant pustule in a person engaged in an occupation by which he is exposed to anthrax bacilli is sufficient to allow a presumptive diagnosis. It must be proved, however, by isolation of the typical organisms and demonstration of their virulence for the mouse or guinea pig. Blood cultures should be made in every case.

The prevention of anthrax involves proper management and disposition of infected animals or their products primarily. Animals suspected of having the disease should be isolated. If they die, they should not be autopsied; the diagnosis can be established by study of an amputated ear. Carcasses should be buried in a slaked lime pit at least 6 feet deep. Several types of vaccine are available for immunization of cows, sheep, and horses, and are effective in preventing the disease.

Proper treatment of contaminated animal products reduces the incidence of human anthrax. Steam and formaldehyde gas, hydrochloride acid and salt, and exposure to hydrogen sulfide have been found to kill the spores. Workers who *handle potentially infectious materials should be required* to wear gloves and to keep all areas of their body covered; removal of dust by proper ventilation is also very important. Vaccination of humans is not successful.

The localized skin lesion of anthrax should not be excised, incised, or treated with strong chemicals. Antibiotic therapy is very effective in most cases. The sulfonamides (full doses) or aqueous penicillin (200,000 units intramuscularly every 4 hours) produce rapid eradication of the organisms, resolution of the pustule, and cure. An occasional strain of the anthrax bacillus is penicillin-resistant. Aureomycin and Terramycin have also been used successfully in the management

phase serums are compared may be diagnostic. Giemsa stains of scrapings obtained from the base of the vesicles reveal giant cells which contain inclusion bodies; the same findings may be detected, however, in herpes zoster and in varicella.

Herpes Zoster

Herpes zoster is a viral infection characterized by inflammatory reactions in the dorsal root and cranial nerve ganglia. Because attacks have been noted in adults after contact with cases of varicella, it has been suggested that the same agent is responsible for both diseases. Although there is considerable laboratory evidence and clinical impression to support this concept, the question is not yet settled.

Herpes zoster very frequently starts without any preceding disease, although many individuals relate a history of upper respiratory manifestations preceding the onset of the skin lesions. In some cases, it is secondary to trauma, irradiation, leukemia, certain tumors of the brain, or exposure to heavy metals. Whether the virus enters the body through the skin from which it reaches the nervous system, or vice versa, is not known.

The incubation period of herpes zoster is usually 7 to 14 days but may be as long as 21 days Fever and malaise are common in the prodrome, but the outstanding symptom is pain. This is often very severe; its cause is usually undetected until the typical skin eruption appears. Erroneous diagnoses of acute appendicitis or pleuritis may be made when the pain involves the abdomen or chest. After 3 to 5 days of prodromal manifestations, the eruption begins to develop. It is distributed along the course of a sensory or cranial nerve, appears in crops, and is arranged in small clusters along the path of the nerve. The lesions are at first vesicular; they then rupture and become covered by a hard, brown crust. In many respects, their evolution is identical with that of the eruption of varicella. Fever of moderate

the inguinal nodes are often enlarged. Vulvovaginitis develops when the female genitalia are affected. All of the localized forms of herpes simplex are characteristically recurrent and may appear an unlimited number of times.

In some patients, lesions of herpes simplex resembling those of herpes zoster (see below) have been observed on the face after section of the trigeminal nerve for the relief of tic doloreux. They have also been described on the legs, arms, trunk and fingers. Although pain has been absent in some cases, sharp, lancinating discomfort has been present in most instances.

The virus of herpes simplex may produce diffuse infection of the skin. In some patients, this is limited to a single area such as the face, and follows a "fever blister". In others, however, the lesions are very widespread. Although it may appear in normal individuals, diffuse involvement is more frequent in patients who have allergic dermatitis, seborrhea, *sycosis vulgaris, impetigo, scabies, or neurodermatitis.* Disseminated herpes simplex occurs most frequently in young children with eczema and produces the syndrome known as Kaposi's varicelliform eruption. It is thought that the virus reaches the skin by way of the blood stream. Youngsters with this disease are usually quite ill and may have a high fever. Hepatitis is frequently present in very young infants; hepatomegaly and jaundice are usually detected. Death may occur.

The diagnosis of herpes simplex is usually made on the basis of the appearance and course of the lesions. The virus can be isolated by inoculation of vesicle fluid into embryonated chicken eggs; this does not prove its implication in the disease being studied, however, because, as pointed out above, it can be recovered from practically all normal people. Serologic studies may not be helpful because of the wide distribution of neutralizing antibody in the general population. However, a four-fold or greater rise in neutralizing or complement-fixing titer when acute and convalescent

has been claimed to be of benefit in reducing the duration and extent of the disease, and decreasing the severity of the pain and incidence of neurologic residua. There is still some question whether treatment with corticosteroids is indicated. The writer has observed striking relief of pain but no effect on the other features of the disease when cortisone has been given. The possibility of intensifying spread and cellular penetration of the virus must always be kept in mind. If this drug is used, the initial dose should be 100 mg. per day for several days; this is then reduced by 25 mg. a day until therapy is discontinued. Every effort must be made to relieve the severe discomfort of herpes zoster. Potent analgesic agents should be given in adequate doses.

North American Blastomycosis

There are 3 types of blastomycosis: (1) North American, caused by *Blastomyces dermatidis*, (2) European, due to *Torula*, and (3) South American, produced by *Blastomyces braziliensis*. The North American variety is most frequently observed in the southern part of the United States. The disease may be primary in the skin or lungs. Cutaneous blastomycosis is most common on the face, neck, or extremities. The initial lesion is a red papule which may be pustulated and which, in time, becomes crusted; it may have a verrucous appearance. Isolated lesions are surrounded by tiny abscesses and break down to form deep ulcers with hard edges. Mild pain is usually the only complaint. There are no constitutional manifestations.

The diagnosis of blastomycosis is based on the characteristic appearance of the lesions. Culture on Saboraud's medium or corn-meal agar of material obtained from one of the skin lesions will yield the organisms. Skin test with *Blastomyces* antigen is positive. The traditional therapeutic agent is a saturated solution of potassium iodide The initial dose is 5 drops 3 times a day, followed by an increase of

degree is often present and persists for 3 to 4 days or longer. The regional lymph nodes are almost invariably enlarged. The pain may become very intense as the disease progresses. It is often quite mild in young children and disappears in a short time. In elderly *persons, severe pain may persist for* many months or even years after the skin lesions have disappeared.

The lesions of herpes zoster with either sensory or cranial nerve involvement are always unilateral. They appear most often on the trunk, but are also observed, in decreasing order of frequency, on the neck, shoulders, arms, lower extremities, and perianal area. Of the cranial nerves affected, the ophthalmic branch of the trigeminal (5th) is the most common, ulcers of the cornea and conjunctiva develop. When the mandibular branch is involved, vesicles occur on the floor of the mouth, buccal mucous membrane, and anterior half of the tongue. Disease of the maxillary branch produces lesions on the uvula and tonsil. The geniculate ganglion may rarely be infected and lead to the development of the Ramsay-Hunt syndrome which is characterized by deep pain in the ear, an herpetic eruption in the external canal, and facial paresis on the affected side. Diffuse herpes zoster involving extensive areas of the skin without segmental distribution is rare. It is observed primarily in patients with leukemia or lymphomas, and resembles chicken pox; pain is characteristically absent.

Most cases of herpes zoster recover within a week or two; scarring may occur at the sites of the lesions. A small number of patients develop complications. These include secondary bacterial infection of the vesicles, permanent facial paralysis *(Ramsay-Hunt syndrome), transient paralysis of an extremity*, hyperesthesia, hypo- or anesthesia, loss of taste, and impairment of vision or loss of sight, a common occurrence when the ophthalmic branch of the 5th nerve is affected.

There is no specific therapy for herpes zoster. None of the antibiotic drugs are of value. The administration of cortisone

sels in the skin. It is proved by isolation of *Sporotrichum* from the lesions by culture on any of the common laboratory media or on Saboraud's or corn-meal agar.

Potassium iodide is very effective in the management of sporotrichosis. Ten drops of a saturated solution of the drug are given orally 3 times a day on the first day and 15 drops 3 times on the second day. The quantity is then increased until 30 to 40 drops are being administered 3 times daily. Therapy is continued for at least 6 weeks after recovery. Stilbamidine given by the method described above (see Blastomycosis) has been reported to cure the disease.

5 drops daily until symptoms of iodism (increased salivation, burning sensation in the mouth, gastric discomfort, and conjunctival irritation) appear. These may not be present until *more than 300 drops* per day are being administered. The dose is then adjusted to the quantity which does not produce an untoward effect and treatment continued for several weeks or months, depending on the clinical response. Stilbamidine has been found to be a very effective agent in the therapy of this disease. The drug is toxic, however, and produces severe 5th nerve damage or widespread sensory loss. 2-hydroxystilbamidine is less toxic; the recommended dose of this agent is 0.1 to 0.5 gm. by intravenous drip once daily for 2 to 3 weeks or longer. Repeated courses of treatment *interspersed with rest periods* may be necessary to effect cure. If leukopenia develops, the drug should be stopped.

Sporotrichosis

Sporotrichosis is observed most often in farmers, laborers, and horticulturists. The causative agent is *Sporotrichum schenkii*. The initial lesion of the disease is located subcutaneously and consists of a hard, rubbery, movable, nodule which is not attached to the overlying skin. As fixation takes place, the skin first reddens and then darkens, becomes necrotic and an ulcer develops; this is the sporothrix chancre. After a few days to weeks, new nodules appear in the subcutaneous area; they are characteristically situated along the course of the lymphatic vessels, which become thickened and cordlike. The secondary lesions also attach to the skin and become ulcerated. Involvement of the skeletal system, widespread dissemination with diffuse lymph node enlargement and rapid death, and infection of the nasopharynx or internal organs are rare complications.

The diagnosis of sporotrichosis is usually suspected on the basis of the characteristic distribution of subcutaneous nodules and ulcerations along the course of the lymphatic ves-

temperature, slight conjunctivitis, and a fleeting morbilliform eruption) which appears 1 to 2 days after exposure and lasts one day or less. Usually, there are no symptoms until the end of the incubation period; some patients may have low grade fever during the entire time. Non-productive cough, rhinitis, conjunctivitis, and fever of varying degree characterize the prodrome which lasts for 2 to 6 days. Physical examination reveals little of significance except for the enanthem which, at first, consists of a series of pin-point elevations connected by a network of minute vessels a fraction of an inch in length on the soft palate. From 5 to 20 of these irregularly spaced dots then become red and the vessels around them dilate to form irregular stellate figures which coalesce and produce reddening of the entire pharynx. The conjunctivitis is usually restricted to the palpebral portion; the sclerae are of normal color. Bluish-gray or white areas may be present on the tonsils; these are Herman spots and are not pathognomonic. Koplik spots are the outstanding manifestation of rubeola. These are usually detectable early in the prodromal period and may persist for several days after the skin eruption has developed. They are small, irregular, bright red lesions with minute bluish-white centers and are present on the buccal mucous membrane (opposite the second molar teeth), on the inside of the lips, and on the inner canthus of the eye in some instances, but not on the soft or hard palate. Koplik spots have also been observed on the mucous membrane of the colon. As the skin rash appears, the buccal eruption loses its discrete character and becomes diffuse. In the late stages of severe cases, the entire mucous membrane is intensely red and studded with innumerable bluish-white specks. The lesions may persist through the entire duration of the exanthem, or decrease markedly as it evolves.

The rash of measles consists of irregular, pink macules and papules which appear first on the face and then spread to the trunk and extremities; lesions are frequently present

CHAPTER XVI

SYSTEMIC INFECTIONS WITH PRIMARY MANIFESTATIONS IN THE SKIN

SYSTEMIC INFECTIONS WITH MACULAR AND PAPULAR (MORBILLIFORM) ERUPTIONS

MEASLES (RUBEOLA)

Measles is a highly communicable virus infection transmitted by way of the respiratory tract. The incubation period is 8 to 12 days. The disease is infectious from the beginning of the prodrome through 5 days after the rash appears. Although all age groups are susceptible, most people have had rubeola by the time they are through adolescence. Infection may take place in utero, if it occurs late in pregnancy, the baby may have a rash at birth or develop it shortly after. Children born of mothers who have had measles are immune for 6 to 9 months.

Measles tends to occur in epidemic form approximately every 2 to 3 years. Its introduction into populations in which it has not been present for many years leads to the development of very widespread outbreaks in which the clinical manifestations are markedly exaggerated, the incidence of complications high, and the fatality rate considerably greater than is observed with sporadic cases.

The virus of measles reaches the blood after it is inhaled into the respiratory tract. This is followed in some but not all individuals by the "fever of infection" (mild elevation of

sions. Encephalomyelitis develops in approximately 1 out of every 800 cases (Chapter XIII). Acute colitis with abdominal pain and bloody diarrhea, or intense laryngeal involvement with obstruction may occur rarely in adults. Electrocardiographic abnormalities may be observed; prolonged conduction and complete heart block have been described. One of the most serious complications of rubeola is thrombopenia; this may be very severe and lead to the appearance of widespread hemorrhages, not only in the skin ("black measles"), but also in all of the internal organs. The number of platelets should be determined in all cases in which there is a "hemorrhagic" rash. Second attacks of rubeola are rare.

There is no specific treatment for measles. The administration of antibiotic agents for the prevention of secondary bacterial infection is without benefit. Cases must be strictly isolated because the index of contagion is 100 per cent. Strictest precautions must be exercised in the sterilization of dishes and the handling of objects with which patients come in contact. Darkening of the room reduces the discomfort from photophobia. Pain in the pharynx, which is often present, may be relieved by saline gargles or the use of analgesic agents. Some physicians give expectorants for the relief of cough; the effectiveness of this is doubtful. Cortisone must be administered when thrombopenia develops, despite the potential risk of a deleterious effect on the infectious process.

Gamma globulin prepared from normal human plasma is very effective in preventing measles or modifying its course, when given to individuals who have been exposed. Children under 2 years of age, older people with chronic or acute disease, and pregnant women should be completely protected; the dose of gamma globulin for this purpose is 0.1 ml. per pound of body weight (maximum of 10 ml. for adults). In other persons, the aim of prophylaxis is modification of the disease. This can be accomplished in most, but

also on the palms and soles. The eruption usually increases in extent and severity for about 3 to 4 days, and becomes confluent in many areas, especially on the face; it may be dark red in color or even hemorrhagic in severe cases. As the rash is developing and spreading, the temperature rises and may reach a height of 105° to 106°. During this period, non-productive cough, which is always present, may be very troublesome. The conjunctivitis, which usually remains limited to the palpebra, may become intense and produce ocular discomfort and marked photophobia. Despite the fact that all patients with measles have a diffuse panbronchitis, the lungs are usually clear on examination; scattered inspiratory rales and a few rhonchi may be detected in some cases. Generalized lymphadenopathy is common; the spleen may be enlarged. After 3 to 5 days, the exanthem begins to fade, the temperature declines, and the respiratory and conjunctival symptoms decrease in intensity. Brown stain persists for some time in the areas of skin in which the rash was present; this is due in part to old hemorrhage and, in part, to inflammatory melanosis. If a patient takes a warm bath, these sites may redden and give the impression of recurrence of the eruption. Branny desquamation occurs in all of the involved areas of the epidermis.

Laboratory studies usually reveal a normal or somewhat decreased white blood count, often accompanied by a relative lymphocytosis. "Atypical lymphocytes" may be present in small numbers. Leucocytosis indicates the presence of a complication such as secondary bacterial infection or encephalitis. Roentgenographic study of the chest discloses increased bronchovascular markings in practically all cases, and suggestive parenchymal infiltrations, probably due to the measles virus, in about 50 per cent.

Secondary bacterial infections are the commonest complication of measles. Pneumonia and purulent otitis media due to the beta-hemolytic streptococcus, pneumococcus, *H. influenzae*, or *Staph. aureus* are the two most frequent le-

mon. The spleen is palpable in about 25 per cent of cases. Irregular, red areas may be present on the buccal mucous membrane during the prodromal and eruptive phases. These are the so-called Forscheimer spots; they are not pathognomonic of rubella.

Leukopenia is usually present; the white blood count is normal in some cases. A relative lymphocytosis is very common. "Atypical" and plasma cells are often observed.

The course of rubella is benign. The rash usually disappears in 2 to 4 days and may leave mild branny desquamation in its place. Enlargement of the lymph nodes may persist for weeks to months after recovery.

Several types of complication may develop in the course of German measles. Encephalitis is the most serious one (Chapter XIII). Thrombopenia occurs rarely and produces widespread hemorrhages. Acute arthritis involving primarily the proximal interphalangeal and the large joints is observed frequently in adolescents and adults, but uncommonly in young children, it usually appears as the eruption is fading, persists for several days, and does not recur. Pain is the only complaint in some cases; in others, changes indistinguishable from those of rheumatoid arthritis are present.

The most important effects of rubella are observed when it occurs during pregnancy. A varying degree of damage to the fetus may take place. Although the incidence of congenitally defective children has been reported as high as 100 per cent when the disease has appeared in the first trimester, the most recent study of this problem reveals a much lower risk. Stillbirth is now thought to occur in 6 to 7 per cent and congenital defects in 14 to 16 per cent of babies born to women who develop German measles during the first or second trimesters; infection in the last 3 months of pregnancy is apparently without danger to the fetus. Among the lesions which have been observed are cataracts,

not all, cases by the administration of 0.02 ml. of globulin per pound of body weight. *Modified measles is characterized* by variable syndromes: rash with fever, fever without an eruption, or a very mild but complete clinical picture. Koplik spots may be absent. The incidence of complications is markedly reduced; encephalitis still occurs, however. Immunity is qualitatively and quantitatively the same as with full-blown rubeola. In order to be maximally effective, gamma globulin must be given not later than 5 days after exposure.

GERMAN MEASLES (RUBELLA)

Rubella is an acute infection produced by a virus which is transmitted by way of the respiratory tract. The incubation period averages 12 to 14 days, but may vary from 10 to 21 days. The disease is infectious from 1 to 2 days before and throughout the duration of the rash.

Prodromal manifestations are not present in every case. When they do appear, they are usually quite mild and consist of slight coryza, low-grade fever, generalized malaise, *and discomfort in the neck and post-auricular areas* due to the enlarging lymph nodes. Lymphadenopathy may develop 1 to 2 days prior to the appearance of the eruption without other manifestations of disease. The exanthem usually appears first on the face and then spreads peripherally over the trunk and extremities. It is made up of discrete, pink, irregular macules. A scarlatiniform eruption may replace it on the second day. The rash is often kaleidoscopic in character, changing its appearance several times during the course of the disease. There is usually only a slight to mild elevation of temperature; fever is entirely absent in some instances. The other outstanding sign of rubella is lymphadenopathy. The post-auricular and suboccipital lymph nodes are very frequently enlarged, somewhat painful, and tender. Generalized lymphadenopathy is com-

The individual lesions are usually pink or salmon colored, slightly raised, usually discrete, and lighter in color than those of measles. Coalescence may occur and produce a blotchy appearance. The rash is most intense on the face and chest, but also appears on the arms, buttocks, and legs; it may be distributed over the entire body. Tiny, punched-out ulcers may be observed on the soft palate in some cases; these are thought to represent the late stage of a vesicular enanthem. Lymphadenopathy is not the rule, although slight enlargement of the nodes in the posterior cervical triangles and suboccipital and postauricular areas have been noted. General manifestations are usually mild. In adults, however, there may be moderately severe myalgia, shaking chills, fever, and sore throat.

The diagnosis of "Boston exanthem" is established purely *on clinical grounds. There are no specific laboratory tests.* Antibiotics are without effect.

Roseola Infantum (Exanthem Subitum)

Roseola infantum is a common exanthematous disorder of children. There is good evidence that it is due to a virus. An agent cytopathogenic for tissue cultures and neutralized by serum obtained after recovery has been isolated from the feces of patients; it is apparently different than the one involved in "Boston exanthem." The disease is almost completely limited to children less than 3 years old, the highest incidence being between 6 and 18 months of age. It may occur, however, in younger babies, in older children, and rarely even in adults. There is no particular sex distribution. Exanthem subitum is only slightly contagious, secondary cases being observed only rarely. Minor epidemics have been described, however.

The onset of roseola infantum is sudden in most instances. Prodromal manifestations may be present in some cases; coryza is frequent but occasionally mucopurulent. Nasal

cardiac abnormalities, of which patent ductus arteriosus is the most common, buphthalmos, improper development of the teeth, and microcephaly.

There is no specific treatment for rubella. Antibiotic agents are without value. Vaccines for active immunization are not available. The most important problem in the prophylaxis of German measles is the protection of pregnant women exposed to the infection. Normal gamma globulin is without effect when given for this purpose. Gamma globulin prepared from plasma obtained from recently recovered cases may prevent the disease when given early in a dose of 10 ml.; this material is not presently available from commercial sources. It has been suggested that, because one attack is almost totally immunizing and second episodes are rare, *all females be exposed to rubella during childhood.*

"Boston Exanthem"

In 1951, a new exanthematous disease which resembles rubella in many respects was described in Boston, Mass. It is due to a virus which produces a cytopathogenic effect in tissue cultures of human embryonic skin or kidney, and probably belongs to the ECHO group.

"Boston exanthem" occurs most commonly in chilren, although it has also been observed in adults. Fever is present *in most cases for 1 to 2 days before skin manifestations* appear. In others, it first becomes apparent as the rash develops, or only after the eruption has reached its height; in some instances, it is observed throughout the course of the disease. The temperature is *101° to 102°* in most cases; some start abruptly with fever of 104° to 105°. Shaking chills may occur in the early stage. The exanthem is variable in intensity and extent. In many patients, the lesions are barely visible, discretely distributed, and do not exceed *8* to 10 in number. In others, they are more diffuse and only slightly elevated. A florid morbilliform rash may be present.

Dengue (Breakbone Fever)

The causative agent of dengue is a virus which is transmitted by *Aedes aegypti*. The incubation period is 3 to 15 days. The earliest manifestations are severe headache, pain in the eyes, generalized muscle aching or intense arthralgia, and prostration. The temperature rises to 104° to 106° within the first few hours and then usually returns quickly to normal. The joint and muscular discomfort is frequently agonizing, and patients are unwilling to attempt walking because of it. Fever recurs on the 5th or 6th day and is of the order of 105° to 106°. A true bradycardia is very commonly noted.

Skin lesions appear twice during the course of the disease. The first or "primary" rash is a diffuse erythema of the face, neck, shoulders, and trunk. It disappears rapidly. On the 5th day, a macular exanthem develops on the hands, arms and legs, but rarely on the face. In some cases no eruption is present; in others, only the terminal one appears. Hemorrhages (primarily epistaxis), diarrhea, or orchitis may occur. The entire course of dengue usually encompasses only one week.

Laboratory studies reveal leukopenia with relative lymphocytosis. There are no specific methods of diagnosis. The presence of the disease is suspected when the characteristic syndrome develops in an individual living in an endemic area.

There is no specific therapy. Relief of the severe pain by the liberal use of potent analgesic agents is indicated. The prognosis for recovery is excellent, death does not occur. Convalescence may, however, be quite prolonged, and mild prostration persists for many weeks Full return to normal may require six or more months.

discharge, edema of the pharynx and uvula, and slight tonsillar exudate are observed. The most striking sign is fever which frequently rises to as high as 105° and 106°. Irritability and malaise are almost constant findings. Convulsions are common. Physical examination usually reveals little or nothing of note at this time. The temperature remains elevated for 2 to 5 days (average 3 days) before the typical rash appears, and may be remittent or intermittent. The eruption usually begins to develop as defervescence sets in; it may, however, be observed 24 hours before the temperature begins to decline, or not until the patient has been afebrile for 24 hours. The lesions are macular, maculopapular or papular; they are light pink, irregular, and discrete (early stage), and are first noted most often on the anterior abdomen, behind the ears, or on the neck. The face *is spared in most cases, although the cheeks may be slightly* involved. The rash on the trunk may become confluent. Slight swelling of the eyelids is sometimes detected. An exanthem consisting of red specks and streaks on the soft palate appears 48 hours before the exanthem in most cases.

The average duration of roseola infantum is 6 days (5 to 9 days). Irritability, anorexia, abdominal pain, cough, headache, earache, arthralgia, and pruritus may be present during the period of the rash. Complications do not occur; one case of hemiplegia thought to be associated with a post-infectious encephalitis has been described.

Laboratory *studies reveal a leukopenia which is usually* most pronounced on the third day of fever. A relative lymphocytosis is the rule. There are no specific diagnostic procedures. The course of the infection, primarily the high fever and convulsions *without detectable physical changes,* and the development of the rash as the fever declines are the important clinical points. The disease is self-limited and always ends in complete recovery. There are no specific therapeutic measures.

can be isolated from the blood and the joint fluid; the media in which they are grown must contain serum.

Rate-bite fever may run its entire course in a few days, or persist for several weeks. The important complications are endocarditis, myocardial abscesses, and destruction of the involved joints.

The diagnosis is suspected when the syndrome described above develops in an individual who has been bitten by a rat or mouse. A history of such injury is not always obtainable, but the infection is most common in persons, meat workers for example, who are exposed to rats in their occupation. The specific etiology is established by isolation of *Streptobacillus moniliformis* from blood or joint fluid. Demonstration of a rising level of serum agglutinins for the organism confirms the diagnosis, the titer reaches its height 1 to 3 months after onset of the disease. Antibody persists for from 5 months to 2 years.

Penicillin is used most often for the treatment of this type of rat-bite fever; 250,000 units of the aqueous benzyl compound given intramuscularly every 6 hours for 10 to 12 days is effective. The tetracyclines, chloramphenicol, bacitracin, and erythromycin have been shown to be curative in experimental infections, clinical experience with these drugs is too limited, however, to allow recommending their substitution for penicillin.

Rat-Bite Fever Due to Spirillum Minus (Sodoku)

Except for a few clinical features and the nature of the causative agent, this variety of rat-bite fever bears a close resemblance to the syndrome produced by *Streptobacillus moniliformis*. The incubation period of *Spirillum minus* infection is 1 to 6 weeks. The site of the rat bite is swollen, painful, tender, and purple in color; the regional lymph nodes are enlarged. Fever is most often relapsing, with 2 to 4 days of elevated temperature being followed by an equal

Rat-Bite Fever

There are two types of rat-bite fever; one is produced by *Streptobacillus moniliformis* and the other by *Spirillum minus*. Both are characterized by fever, arthritis, and skin eruptions. They differ somewhat in their course and treatment.

Rat-Bite Fever Due to Streptobacillus Moniliformis (Haverhill Fever)

Rat-bite fever due to *Streptobacillus moniliformis* is also known as Haverhill fever. Although most cases follow the bite of rats or mice, one epidemic has been traced to the ingestion of contaminated milk. The organisms are pleomorphic, gram-negative bacilli; filamentous forms, short cells, and L-forms are often observed. When growing in broth, they produce "puff balls" which lie on the bottom of the flask.

The incubation period is 3 to 7 days. The onset of the disease is sudden, with elevation of temperature, headache, and malaise; shaking chills are common. The fever may be intermittent or remittent. Occasionally, it is relapsing and 2 to 3 days of normal temperature are interspersed with several days of fever. Swelling, pain, and tenderness of the large joints appear during the first week; destruction of cartilage may occur. Moderate to severe muscle pain is present. The site of the rat bite is moderately inflamed and the regional lymph nodes are enlarged. There are no local lesions in cases which result from the ingestion of milk. Almost all patients develop a red, papular rash which is concentrated mainly around the joints; the eruption is diffuse and resembles measles in some instances.

The white blood count is usually elevated to 10,000 to 15,000 per mm^3, although it may be normal. The organisms

irregular, pink macules which later become papules; uncommonly, they are hemorrhagic in appearance. The eruption appears on about the fifth day of fever and persists for 4 to 8 days; in mild cases it may be fleeting. Stupor, coma, prostration, or a muttering delirium develop in the second week of illness in severe cases. Signs of meningeal irritation may be present but the cerebrospinal fluid is usually normal; it may contain a small excess of lymphocytes. Splenomegaly occurs in 25 per cent of patients. Photophobia and conjunctivitis are common, but not as marked as in other rickettsial infections. Elderly patients may exhibit renal failure and hypotension.

The prognosis for recovery in untreated cases of murine typhus is good, death occurring only infrequently.

Murine typhus is suspected in patients living in areas where the disease is endemic, who develop fever, severe headache, and a maculopapular rash The diagnosis is proved by demonstration of a rising titer of complement-fixing antibody or agglutinin for *Rickettsia mooseri* in serums obtained in the acute and convalescent phases of the disease.

Aureomycin, Terramycin, and chloramphenicol cure endemic typhus. The initial dose of the first two agents is 25 mg. per Kg.; this is followed by 25 mg. per Kg. per day divided into 4 equal quantities The first dose of chloramphenicol is 50 mg. per Kg , thereafter, 0 5 gm. is administered orally every 4 hours. Treatment should be continued for 7 to 10 days. There are no specific methods of immunization. The most effective prophylactic measure is elimination of rats. DDT should be used in infested areas to eradicate the fleas

Chronic Meningococcemia and Gonococcemia

Macular eruptions are a common feature of chronic meningococcemia and gonococcemia. Petechial or purpuric

period of defervescence. A diffuse rash consisting of large red or purple lesions appears and may become confluent. The white blood count may be elevated or normal. Biologic false positive tests for syphilis are common. One case of endocarditis has been described.

The diagnosis of *Spirillum minus* rat-bite fever is suspected on the same basis as *Streptobacillus* infection. It is confirmed by isolation of the organism. This is accomplished by intraperitoneal injection of patient's blood into guinea pigs; the blood of the animal is examined by dark field microscopy 1 to 3 weeks later. Arsenicals are used at present for the treatment of the disease; the effectiveness of penicillin remains to be determined.

Endemic (Murine) Typhus

Murine typhus occurs primarily in the Southeastern and Gulf coast states of the United States and is most common in the summer and fall. It is due to *Rickettsia mooseri.* The organism is transmitted to man from its reservoir in the rat by the bite of the rat flea.

The incubation period of murine typhus is 8 to 16 days. Prodromal manifestations are present for about 5 days before the skin eruption appears. The outstanding symptoms are moderate to severe headache, backache, and chilly sensations. The disease may start with a shaking chill. The temperature is always elevated and usually ranges between 102° to 104°, although it may be as high as 105° to 106° in children. Nausea, vomiting, and arthralgia are frequent. The prodrome may be very mild in some cases; in others, it is severe, weakness and prostration being striking. The rash of murine typhus appears initially in the axillae and on the inner surface of the arms, but quickly becomes generalized. It is most intense on the upper abdomen, shoulders, chest, arms and upper legs, and sparse on the face, palms, soles, and extremities. The individual lesions are at first discrete,

SCARLET FEVER

The rash is the only feature which distinguishes scarlet fever from streptococcal tonsillopharyngitis. The appearance of the exanthem depends on the ability of the invading organism to elaborate erythrogenic toxin, and the absence of antitoxin for this substance in the host. Most group A streptococci produce erythrogen. If an individual without antitoxic immunity (Dick positive) is infected by such an organism, he develops a sore throat and an eruption—scarlet fever; the patient whose blood contains antitoxin (Dick negative) gets only tonsillopharyngitis.

The incubation period of scarlet fever averages 48 to 72 hours. Occasionally the disease may appear within as short a period as 18 hours or as long as 7 days after exposure.

The manifestations of the acute phase of scarlet fever can be divided into two main groups on the basis of their pathogenesis. First, are the symptoms and signs which result from tissue injury at the portal of entry of the beta-hemolytic streptococcus. These are localized to the site of multiplication of the organisms; they are fever, malaise, generalized muscle aching, headache, and occasionally diarrhea in children. Second, are the changes produced by the toxins, mainly erythrogen, which are absorbed from the area of infection; these include the rash, as well as malaise, headache, nausea and vomiting, fever, generalized lymphadenopathy, latent jaundice, mild anemia, mild hematuria, and abnormalities of the tongue.

Scarlet fever occurs most frequently between the ages of 2 and 10 years. The neonatal infant is immune. Resistance in this age group is not related to the presence of antitoxin in the mother and persists for about 3 to 6 months. The disease is uncommon in adolescents and adults; contact with the group A beta-hemolytic streptococci leads most often to

rashes are, however, more frequent. These diseases are discussed below in the section on "Petechial or Purpuric Rashes".

Differential Diagnosis of Maculo-Papular Rashes

The morphology of a rash has very little specific diagnostic significance. Maculo-papular eruptions are observed not only with infectious but also with non-infectious disorders. Listed below are a number of conditions which must be considered when the etiology of this type of exanthem is not clear. In many of these, the rash varies in type and is not always maculopapular; in some, the early lesions are morbilliform and the later ones petechial or purpuric.

CONDITIONS IN WHICH MORBILLIFORM ERUPTIONS MAY BE USED

Rubeola
Rubella
"Boston exanthem"
Roseola infantum
Dengue
Infectious mononucleosis
Infectious hepatitis
Rat-Bite fever
Meningococcemia
Gonococcemia
Staph. aureus infections
Tuberculosis
Typhoid fever
Paratyphoid fever
Diphtheria
Syphilis
Murine typhus
Typhus fever (epidemic)
Rocky Mountain spotted fever
Trichinosis
Rheumatic fever
Reactions to many drugs
Food allergy
Serum sickness
Contact dermatitis

Systemic Infections with Punctate-Erythematous (Scarlatiniform) Eruptions

Diffuse punctate erythematous rashes are observed most often in scarlet fever, although they may also develop in other infectious or even in non-infectious diseases.

long linear extravasations of blood, are present most prominently in the antecubital and axillary folds. Tourniquet tests are commonly positive when the disease is severe and indicate the generalized increased capillary fragility. Enanthem is present on the soft palate and has the same general features as the skin lesions. Dermatographia is sometimes striking. When the exanthem is very severe, it may consist almost entirely of small purpuric spots superimposed on the generalized erythema, bacteremia is only very rarely present in these cases. The eruption may be vesicular; this is most common on the skin of the lower anterior abdominal wall. In mild cases, the rash may first be noted on the trunk; it may be restricted to a relatively small area, light in color and not accompanied by bleeding lines. The exanthem is frequently atypical in Negroes because of the dark pigmentation of the skin; it may consist only of elevated papules resembling "goose-flesh."

The rash of scarlet fever persists for about 4 to 5 days in the average case, and 24 hours or less in the mild one, its duration is not influenced by chemotherapy. Desquamation appears as the exanthem begins to fade, usually starts on the pinnae, and spreads in the same fashion as the eruption. Shedding of the skin may last for days, or uncommonly for weeks, it is not related to continuing infectivity. The desquamate on the trunk usually has a "branny character"; the skin of the hands and feet comes off in large flakes or sheets.

In addition to the pharyngitis and rash, there are several other striking features of scarlet fever. Generalized lymphadenopathy is the rule in the acute phase. Although the lymph nodes at the angle of the jaw are usually large and tender, lymphadenopathy is often most marked in the inguinal region. Splenomegaly is present in from 5 to 10 per cent of patients at the beginning of the illness. The hands and feet may be red and swollen. Jaundice is observed rarely and is probably due to a "toxic" hepatitis.

As scarlet fever begins, the tongue is usually covered by

the development of pharyngitis or other local lesions without a generalized eruption.

Within 48 to 72 hours after *Strep. pyogenes* is implanted in the host, the first manifestations begin to appear. In the majority of cases, the streptococci invade the upper respiratory tract. There is no reason for classifying scarlet fever on the basis of the location of the portal of entry; the terms "surgical," "burn," "puerperal" and "enteric" scarlet fever should not be used because the clinical picture in all of these is similar. The earliest symptoms in patients who acquire infection by way of the respiratory tract are pharyngitis and fever. The temperature rises very rapidly and may reach 103° to 104°. There may be only slight fever in mild cases. Shaking chills are uncommon. The appearance of the pharynx has been described in Chapter VI. Headache, malaise, generalized aching, diffuse abdominal discomfort, nausea, and vomiting are features of the moderate to severe illness. Physical examination at this time reveals a flushed, warm skin, without rash, and a varying degree of pharyngitis.

The interval between the development of pharyngeal involvement and the appearance of the rash is usually 24 to 48 hours. The distribution and morphologic characteristics of the exanthem vary considerably with the severity of the disease. The eruption usually appears first on the sides and front of the neck, then spreads down over the chest and abdomen, and finally covers the extremities, the distal portions being the last involved; the palms and soles are spared. In the average case, the rash is a diffuse erythema with superimposed punctate red spots, 1 to 2 mm. in diameter, and blanches on pressure. It is most intense in the inguinal, antecubital, abdominal, and axillary folds The skin of the face is usually clear but shows marked flushing, particularly of the cheeks, with circumoral pallor; in about 10 per cent of patients, particularly those with fair complexions, there is a facial eruption. "Bleeding" or Pastia's lines, short or

or V orally every 8 hours for 10 days abruptly terminates the acute phase of the disease and completely prevents the development of suppurative complications; it has been suggested that the incidence of rheumatic fever and glomerulonephritis is also appreciably reduced. Alternate methods of treatment are (1) a single daily intramuscular injection of 300,000 units of procaine penicillin for 10 days, and (2) the parenteral administration of one dose of 1,200,000 units of Bicillin. In patients sensitive to penicillin, erythromycin, 250 mg. orally every 6 hours, is effective.

Scarlet fever can be prevented by the administration of increasing quantities of erythrogenic toxin at periodic intervals. It must be stressed, however, that this type of immunization does not protect against invasion by beta-hemolytic streptococci and the development of suppurative and non-suppurative complications. Because of this and because the isolation period for the disease has been markedly shortened or completely eliminated in most communities, protection against the erythrogenic toxin is of little or no importance. The best prophylactic procedure for scarlet fever is the administration of penicillin as described in Chapter VI.

STAPHYLOCOCCAL SCARLET FEVER

Some strains of *Staph. aureus* elaborate an erythrogenic toxin antigenically similar and indistinguishable from that produced by group A beta-hemolytic streptococci. Infection with these organisms is followed in some instances by a skin eruption identical with that present in scarlet fever. As a rule, the staphylococcal diseases in which such an exanthem appears are deep-seated—osteomyelitis, pneumonia, meningitis, etc. Whether the syndrome appears with pharyngitis is questionable. Since staphylococci are present in the throats of most normal persons, it is impossible to attach causal significance to their demonstration in cases with

a white coat through which reddening and hypertrophy of the papillae are visible; this is the "strawberry" tongue. During the next 3 to 4 days, the glossal coating is gradually lost and the surface is beefy red in color and studded with markedly enlarged papillae; this is the "raspberry" tongue. Desquamation begins shortly. At the end of a week, the tongue is pale and smooth; it resumes a normal appearance in about 2 to 3 weeks. The "strawberry" tongue is not pathognomonic; it is observed in a number of other infections. The "raspberry" tongue has greater diagnostic significance.

The laboratory findings and *complications of scarlet fever* are the same as those of streptococcal tonsillopharyngitis (Chapter VI).

The presumptive diagnosis of scarlet fever is usually made on the basis of its clinical features. It can be proved by (1) isolation of group A beta-hemolytic streptococci from the pharynx, (2) a positive Schultz-Charlton reaction, and (3) conversion of a Dick positive to a negative reaction. The serological methods of value in proving the presence of streptococcal infection are discussed in Chapter VI.

The Schultz-Charlton test is performed by injecting 0.1 ml. of potent streptococcal antitoxin endermally in an area where rash is present. "Blanching" around the site of injection 24 hours later indicates that erythrogenic toxin is responsible for the eruption.

The Dick test is carried out by injecting 0.1 mg. of "scarlet fever toxin" containing 1 skin test dose into the skin. The development of an area of reddening 1 cm. or larger in diameter 24 hours later is considered a positive reaction and indicates lack of antitoxic immunity. The test is usually positive during the first 1 to 3 days of the disease; it becomes negative in 1 to 2 weeks. Conversion of the reaction from positive to negative is of help in the diagnosis of scarlet fever.

Penicillin is the drug of choice for the treatment of scarlet fever. The administration of 200,000 units of penicillin G

most evident on the face and extremities. The rash may be sparse and discrete or very widely disseminated and confluent. The macules are rapidly transformed to shot-like papules.

About the 6th day of the disease, all of the lesions have become vesicular. They are often umbilicated and multilocular. The lesions become turbid and pustular after 2 to 3 days; fever recurs at this time and may reach a high level. Drying and crusting take place during the next 10 to 12 days. The crusts separate in about one month, leaving pitted scars.

One of the most characteristic features of smallpox is that the lesions in one area of the skin are all at the same stage of development. The rash never appears in crops as it does in chicken pox. The palms and soles are always involved where the individual lesions have a hard, nodular, shotty feeling, and are sometimes surrounded by a dark purple zone ("mahogany plaque"). Lesions are often present on the mucous membranes of the mouth, tongue, nose, pharynx, larynx, trachea, bronchi, genitalia and conjunctivae, but are usually not detected in the axillae, a site in which they are practically always observed in chicken pox.

The severity of smallpox is variable. Confluent rashes may be present. In some cases, petechial and purpuric lesions develop on the second day and are accompanied by hemorrhage from various mucous membranes, death usually occurs within 6 days. If a strain of virus of relatively low virulence is involved, *alastrim* results, this is a very mild form of smallpox in which the rash is sparse and pustular lesions are not present. When the disease appears in partially immune individuals, the prodromal manifestations and eruption are of minor or moderate severity and a secondary rise in temperature does not accompany the pustular stage; this syndrome is known as *varoloid*. In general, smallpox is most severe in young children, in elderly individuals and in primitive races.

pharyngitis and a scarlatiniform rash; these may be instances of viral or streptococcal disease.

The only method of establishing the diagnosis of staphylococcal scarlet fever is isolation of the organisms and proving that they elaborate an erythrogenic toxin. The treatment is the same as for other types of staphylococcal infection.

CONDITIONS IN WHICH SCARLATINIFORM ERUPTIONS ARE PRESENT

Scarlet fever due to *Strep pyogenes*
Infections with erythrogenic toxin-producing strains of *Staph. aureus*
Rubella
Infectious mononucleosis
Infectious hepatitis
Sunburn
Mercury poisoning
Gold poisoning
Sensitivity to quinine or atropine

Systemic Infections with Vesicular or Bullous Eruptions

SMALLPOX (VARIOLA)

Smallpox is a highly contagious virus infection transmitted by way of the respiratory tract. The incubation period is 11 to 12 days, *with limits of 8 to 21 days.*

Prodromal manifestations are usually present for 3 to 4 days. They start very abruptly and consist of chills, fever up to 104°, headache, nausea, vomiting, and severe backache. A fleeting erythematous or hemorrhagic rash may be present. On about the fourth day, the characteristic exanthem begins to develop; there is a decline in the temperature and the patient feels better at this time. The eruption which consists of red macules appears first on the face, and then spreads to the arms, trunk, and legs where it is present mainly below the knees; it is centrifugal in character, being

smallpox must be strictly isolated in the hospital. All articles with which they come in contact must be completely disinfected. All of the people associated with the patient prior to his hospitalization, and all the doctors, nurses and other individuals who are concerned with his care must be vaccinated.

Smallpox is easily preventable. Inoculation of cowpox virus produces almost complete immunity; mild variola may occur in vaccinated persons. Revaccination should be carried out every 6 to 7 years. It has been suggested that a successful "take" in infancy, and "immune" response at 6 years of age, and an "accelerated" reaction at 16 years gives protection for life. In the face of an epidemic, all individuals should be immunized. Vaccination is best carried out initially during the first year of life because the incidence of post-vaccinial encephalitis is minimal at this time.

Four types of response are produced by cowpox vaccination: (1) primary vaccinia, (2) accelerated reaction, (3) immune response, and (4) no "take." The features and course of a primary "take," the reaction in non-immune individuals, are described below. *Accelerated reactions* (vaccinoid) appear in subjects with a low level of immunity. A papule develops at the site of inoculation after 3 days. The vesicle and the area of inflammation around the lesion are smaller than in primary "takes," the maximum intensity of the reaction appearing between the 4th and 8th day. The resulting scar is small and may disappear after 1 or 2 years *"Immune" responses* occur when a high level of immunity is present as *a result of previous vaccination; they are characterized* by a small area of reddening which is maximal 1 to 2 days after inoculation and a small papule which usually appears on the 3rd day. Vesicle formation does not occur, and there is no constitutional reaction. When no lesion of any type develops after vaccination, the procedure should be repeated because *"no take"* indicates improper technic or a poor vaccine. Disinfectants should not be applied to the skin prior to inocula-

Variola is contagious from the time of first appearance of prodromal manifestations until all crusts disappear. Crusts removed from the lesions and stored in a bottle have remained infectious for longer than a year. One attack of the disease usually confers permanent immunity; second attacks are rare.

The most important complication of smallpox is secondary bacterial infection of the skin lesions. The organisms most commonly involved are *Staph. aureus* and the beta-hemolytic streptococcus, although other bacteria are sometimes responsible. A diffuse, hemorrhagic, necrotizing bronchopneumonia due to the virus is observed occasionally.

The presumptive diagnosis of smallpox is made on the basis of the characteristic prodrome and evolution of the rash is an unimmunized individual. There are several methods for establishing the presence of variola virus. (1) Inoculation of vesicle fluid into embryonated chicken eggs produces typical pocks in 2 to 3 days; the identity of the virus is confirmed by neutralization tests. (2) Injection of fluid from a lesion into the cornea of a rabbit leads to the appearance of ulcers; biopsy discloses characteristic Guarnieri bodies. (3) Stains of scraping of the lesions made by the Paaschen method reveal typical elementary bodies. (4) Vaccination of the recovered patient produces an "immune response."

The prognosis in smallpox is guarded; the fatality rate varies from 1 to 50 or 60 per cent, the largest number of deaths occurring in young children, old people, primitive races, and with the hemorrhagic and purpuric forms of the disease.

The antimicrobial agents are without effect in altering the primary manifestations of smallpox. The administration of analgesics, antipruritic drugs, and antibiotics, if secondary bacterial infection is present, constitute the main points in treatment. Whether the risk of bacterial invasion is reduced by chemoprophylaxis is an unsettled question. Patients with

Diffuse Vaccinia

Very infrequently, inoculation of cowpox vaccine is followed by the development of a widespread vesiculo-pustular eruption which may resemble smallpox or severe chicken pox. This is diffuse cowpox and is probably secondary to the viremia which always accompanies the "primary take"; the reason for its occurrence in only an occasional patient is not known. In the cases which the writer has observed, multiple lesions have appeared in many areas of the skin about 8 to 10 days after vaccination. Fever of varying degree has always been present. The disseminated lesions undergo the same series of changes as the one which appears at the site of inoculation; they are, however, of lesser intensity and heal without scarring in most instances.

The diagnosis of diffuse cowpox is suspected in patients who develop a widespread vesicular eruption approximately one week after they have been vaccinated against smallpox. It is confirmed by inoculation of vesicle fluid into embryonated eggs; typical "pocks" appear on the amniotic membrane. The exact identity of the virus is established by means of neutralization tests with specific antiserums, using embryonated eggs as the test animals.

Eczema Vaccinatum

Children or adults with eczema may develop diffuse cowpox after vaccination or following contact with an individual who has a "primary take." The eruption may be the result of viremia and not due merely to scratching of the pruritic skin. It is often very extensive. High grade fever and other general manifestations of severe infection are frequently present. Death occurs in some cases. The most important differential diagnosis is Kaposi's varicelliform eruption (Chapter XV). The two diseases can be distinguished only on the basis of appearance of the inclusion bodies demonstrable in biopsy specimens or Giemsa-stained smears of

tion because they may kill the virus; cleansing with acetone is sufficient.

VACCINIA (COWPOX)

The "Primary Take"

The commonest lesion of cowpox is the "primary take" which is produced in the process of immunization against smallpox. Itching appears in the area of inoculation after 2 to 3 days. By the 3rd to 4th day, a red papule develops which is transformed into a vesicle 1 to 2 days later. This lesion becomes umbilicated and multilocular at the end of a week, at which time it is surrounded by a considerable area of swelling or redness and is becoming pustular. It begins to dry after about 12 days and becomes covered by a brown crust. The redness and edema gradually clear and the "scab" falls off about 3 weeks after inoculation, leaving the characteristic pitted scar.

Fever of varying degree may accompany the vesicular and pustular stages of the "primary take"; the temperature may reach 103° to 104°, and chilliness may be present. In severe reactions, the periphery of the initial lesion is sometimes surrounded by a number of small vesicles. The axillary nodes on the inoculated side may become enlarged, painful, and very tender. Secondary bacterial infection, often due to *Staph. aureus,* sometimes develops. Treatment with appropriate antibiotic agents is indicated in these cases. Generalized morbilliform, scarlatiniform, or purpuric rashes are rarely observed. Thrombopenia is a rare complication. The most serious untoward effect of smallpox immunization is encephalitis (Chapter XIII). Multiple, discrete lesions resembling the "primary take" may be produced by autoinoculation resulting from scratching; infection of the eye may endanger sight. Children with eczema should not be vaccinated. Eczematous individuals living in a family with a vaccinated child must guard themselves carefully against contact.

mouth, tongue, pharynx, and hard and soft palates are frequently involved. In severe cases, lesions are also present in the tracheobronchial tree and esophagus.

The vesicles become cloudy 2 to 3 days after they appear; the fluid is usually sterile. A brown crust covers them in about a week; this may drop off spontaneously in a few days or persist for weeks and require manual removal.

The most important feature of chicken pox is the manner in which the eruption develops. New crops of lesions continue to appear for 4 to 5 days, sometimes for as long as 7 to 8 days, after the disease starts. Because of this, all stages of the rash—macules, papules, clear and clouded vesicles, and crusts—are detectable in any given area of the skin. This is the most helpful point of differentiation from variola.

Most cases of chicken pox are mild; constitutional manifestations are usually moderate. In some adults, however, the general reaction is very intense and produces a high temperature, chills, severe generalized aching, headache and backache. Fever does not appear with clouding of the vesicle fluid, as is the case in smallpox. The duration of the disease is 7 to 10 days. Scarring does not occur unless secondary bacterial infection has been present.

The white blood count in varicella is usually normal or low; there may be a relative lymphocytosis

Chicken pox is practically always benign. Death is rare and occurs only when such complications as diffuse visceral involvement, pneumonia, or encephalitis develop, it is most frequent in neonatal children who are most susceptible to widespread invasion.

The commonest complication of chicken pox is secondary bacterial infection of the skin lesions; suppuration takes place and, in some cases, may be followed by bacteremia. The organism most often involved is *Staph. aureus.* A bullous eruption may replace the vesicular one (*varicella pemphigoides*); in these cases, the temperature is very high, the

vesicle fluid, and by neutralization tests with specific antiserums.

There is no specific treatment for any form of generalized vaccinia. Patients should be isolated until the rash has disappeared. Chemoprophylaxis is of no benefit. Secondary bacterial infections must be treated with appropriate antibiotic agents.

Chicken Pox (Varicella)

Chicken pox is a very common viral infection.

The incubation period of varicella averages 12 to 14 days, with limits of 10 to 20 days. Prodromal manifestations are often absent in babies. In most other patients, the appearance of the rash is preceded by low grade fever, general malaise, and headache for 1 to 2 days. Some adults have intense backache, high fever, and prostration suggestive of the prodrome of smallpox. Abdominal pain simulating appendicitis may be present in children before the exanthem develops.

The rash of varicella usually appears abruptly and spreads rapidly. Although they may be observed on any area of the skin, the earliest lesions are often noted on the trunk. The first stage is often a macule which quickly becomes a papule. The latter are rapidly transformed into vesicles which contain clear fluid and are surrounded by a narrow areola of inflammation. Unlike smallpox, the eruption is centripetal in distribution and is most marked on the chest and abdomen; the face and extremities are not spared, however, and lesions are frequently present on the palms, soles, and scalp. The vesicles may be multilocular or umbilicated but are superficially situated and do not have the "shotty" feeling of variola except on the hands and feet. On the trunk they are often distributed along the lines of cleavage of the skin and are elongated into an elliptical shape. Rash is often noted in the axillae. A varying degree of pruritus is common. The mucous membranes of the

are of no value. Because of its high degree of infectivity, patients should be isolated and disinfection of fomites carried out. Calamine lotion relieves the pruritus which is severe in some cases. *Saline irrigations* of the throat and mouth and analgesics are helpful in decreasing the discomfort due to the mucous membrane lesions. Secondary bacterial infections must be recognized promptly and treated with appropriate antimicrobial agents; they are not prevented by chemoprophylaxis. There is no therapy for post-varicella encephalitis or primary varicella pneumonia.

Rickettsialpox

Most cases of rickettsialpox have been observed in New York City, although some have been detected in other areas. The infection is due to *Rickettsia akari* which is transmitted from mice, the reservoir of the organism, to man by the bite of a mite.

Seven to 10 days after exposure, a round, firm red papule appears at the site of the mite bite; this increases in size and is replaced by a hard, deep-seated vesicle varying from 0.5 to 1.5 cm. in diameter and containing clear fluid which later becomes cloudy. The lesion gradually shrinks, becomes dry, and is covered by a black eschar which eventually drops off leaving a small scar. Enlargement and tenderness of the regional lymph nodes are common. The average duration of the primary lesion is about 3 weeks, it occurs most often on the covered parts of the skin, but may also appear on the neck, face, arms, and dorsa of the hands or feet. There are usually no constitutional manifestations, and the patient may be totally unaware of this phase of the disease.

The second stage of rickettsialpox begins about one week after the development of the localized vesicle, although it may be delayed for as long as 17 days or occur as early as 3 to 4 days. The onset is abrupt, and the most frequent manifestations are fever which rises rapidly to 103° to 104°, chills

general manifestations are severe, and death may occur. Hemorrhagic lesions may be present in varicella; although these are most often not related to disorders of the clotting mechanism, the possibility of thrombopenia, a rare complication, must always be ruled out. Gangrene of the skin centering in the lesions, most common on the scrotum, may occur in marantic infants. Orchitis is observed rarely.

One of the most important complications of chicken pox is pneumonia. This may be due to the virus itself or to secondary bacterial invasion. Primary varicella pneumonia does not occur in children although viral laryngotracheobronchitis may be observed; bacterial infection of the lungs is not rare. In adults, on the other hand, primary varicella pneumonitis is the commonest pulmonary lesion and is not as rare as is suggested by the small number of cases reported in the literature. Most of the patients who develop this complication have severe and often hemorrhagic rashes. Cough is common and usually non-productive. Chest pain, dyspnea, or asthmatic breathing occur in 50 per cent of cases. Examination of the chest may be totally unrevealing or disclose changes consistent with a lobar or diffuse process. X-ray study usually reveals widespread, nodular infiltration. Death may occur.

Encephalitis develops in 1 out of every 10,000 cases of chicken pox and has a fatality rate of 5 per cent (Chapter XIII). Myocarditis with electrocardiographic changes, anatomically-demonstrable damage, or cardiac failure is a rare complication. It has recently been reported that patients exposed to varicella while receiving cortisone for some other disease develop very severe infection which is often widely diffuse, produces involvement of internal organs, and frequently terminates fatally.

The diagnosis of chicken pox is made on the basis of its clinical features. Most important is differentiation from smallpox; this has been discussed above.

There is no specific treatment for chicken pox; antibiotics

normal in about 2 days. There are no specific prophlactic measures; elimination of mice from buildings reduces the incidence of the disease.

Differential Diagnosis of Vesicular and Bullous Eruptions

There are a number of infectious and non-infectious disorders in which vesicular and bullous rashes occur. Although the exanthem may be papular or macular in the beginning, the outstanding feature at the height of the disease is a fluid-filled lesion.

CONDITIONS IN WHICH VESICULAR OR BULLOUS ERUPTIONS ARE PRESENT

Variola	*Rickettsialpox*
Varicella	Pemphigus
Vaccinia	Drug allergies
Eczema vaccinatum	Penicillin sensitization
Herpes simplex—diffuse	"Id" reactions
Herpes zoster—diffuse	*Erythema multiforme exsudativum* (Stevens-Johnson disease)
Kaposi's vericelliform eruption	Dermatitis herpetiformis
Foot and mouth disease	Epidermolysis bullosa
Typhoid fever—vesiculated "rose spots" in severe cases	Hydroa aestivale
Impetigo	Bromodermia
Ps. pyocyaneus bacteremia	Iodermia
Congenital syphilis	

Systemic Infections with Petechial and Purpuric Eruptions

BACTEREMIA

Petechial and purpuric eruptions are present with some types of bacteremia. The organisms primarily responsible for the infections in which such eruptions occur are *Staph. aureus*, the beta-hemolytic streptococcus, and the meningococcus which is the commonest cause of this type of

or chilly sensations, headache, backache, generalized muscle aching, and lassitude. Photophobia, anorexia, nausea, vomiting, and vertigo are occasionally present. Either at the beginning of the second stage or within 1 to 2 days, a discrete, erythematous, maculopapular eruption develops. The lesions may be sparse or abundant, and are usually first detected on the arms, legs, abdomen, back, chest or face; they may appear on the soft palate or tongue but are not present on the palms or soles. There is no typical pattern of distribution. Pruritus is absent. Within 1 to 2 days, each papule is topped by a firm vesicle which contains clear fluid; these gradually dry and become covered by a black crust which falls off without leaving a scar. The lesions may be confused with those of chicken pox. The average duration is 4 to 7 days; it may be only 2 to 3 days in mild cases and as long as 10 days in severe ones. All patients recover. There are no complications.

The white blood count in rickettsialpox is either normal or decreased; relative lymphocytosis is common. When leukopenia is present, the number of white blood cells returns to normal in about 2 weeks after the onset of fever.

The diagnosis of rickettsialpox is usually made on the basis of the clinical course of the disease. The main points of differentiation from chicken pox are as follows: (1) The lesions of rickettsialpox do not appear in crops, and (2) a primary lesion does not precede the diffuse eruption of varicella. Detection of a significant increase (at least 4-fold) in titer of complement-fixing antibody or agglutinin for *R. akari*, when serums obtained in the acute and convalescent phases of the disease are compared, is specifically diagnostic. Proteus agglutinations are negative.

Rickettsialpox responds to treatment with chlortetracycline (Aureomycin), oxytetracycline (Terramycin), or chloramphenicol (Chloromycetin). The dose of each of these drugs is 0.25 to 0.5 gm. orally every 6 hours for one week. With chemotherapy, the temperature usually declines to

scribed. The rash usually fades within 36 to 48 hours after it appears, leaving discolored bluish-red areas. Enlargement of the spleen is common. The regularity with which the eruption recurs and slowly disappears with subsiding fever, headache, and joint pains is characteristic of chronic meningococcal sepsis.

Among the complications which occur are endocarditis, empyema, acute glomerulonephritis, and meningitis. The disease may last for from several weeks to several months with an average of 3 months. In some instances it terminates with the development of meningeal infection; in others, it heals without specific treatment. The prognosis is very good; 75 to 90 per cent of cases recover, unless endocarditis or meningitis appear.

The diagnosis of chronic meningococcemia is suspected on the basis of the clinical course of the disease and confirmed by isolation of the organism from the blood stream. The treatment is the same as for meningococcal meningitis (Chapter XIII).

Chronic gonococcemia produces a clinical picture identical to that of chronic meningococcemia. The focus of infection is usually in the genital tract. The most important complications are acute endocarditis or suppurative arthritis. The diagnosis is established by isolation of gonococci from the blood stream. The therapy of choice is the injection of 250,000 units of crystalline benzyl penicillin G intramuscularly every 6 hours for 10 to 12 days If endocarditis is present, the quantity of drug used should be doubled and treatment continued for a minimum of 4 weeks.

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever occurs in many areas of the United States usually in the late spring and early summer. It is due to *Rickettsia rickettsi* which is transmitted to man by the bite of the wood or dog tick. The insect must remain

rash. The skin lesions associated with staphylococcal bacteremia are often macular, nodular, or pustular but may also be hemorrhagic. Petechiae and purpura are the usual findings when group A beta-hemolytic streptococci are circulating in the blood stream; no rash is present in some cases. The same type of exanthem is noted in patients with subacute bacterial endocarditis due to *Streptococcus viridans* and non-hemolytic streptococci; it is the result of capillary obstruction and hemorrhage secondary to the deposition of emboli in the skin. The possibility of acute bacterial endocarditis must be considered in all instances of staphylococcal or beta-hemolytic streptococcal bacteremia. Thrombocytopenia secondary to bone marrow depression must be ruled out whenever hemorrhagic eruptions appear in the course of severe bacterial or viral infections.

The diagnosis of bacteremia can be established only by isolating the responsible organism from the blood. The type of treatment depends on the nature of the bacteria and their sensitivity to various antimicrobial agents. The use of corticosteroids in addition to antibiotics is recommended for the management of the secondary thrombopenias.

Chronic Meningococcemia and Gonococcemia

The meningococcus may rarely produce chronic infection. The onset of this disease is usually sudden with fever, chills, headache, joint pains, and a rash. The fever is most frequently intermittent daily, but may resemble the temperature course of tertian or quartan malaria, or occur in 4 day cycles. The eruption usually appears in the first week, fades, recurs with each bout of fever, and is often accompanied by polyarthralgia which may be migratory. It may be of the erythema multiforme type with tender nodules 0.5 to 1 cm. in diameter, and is present on the extremities, trunk and even on the face. Petechial and purpuric lesions are common; herpetic and lenticular "rose spots" have been de-

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Rocky Mountain spotted fever occurs in many areas of the United States usually in the late spring and early summer. It is due to *Rickettsia rickettsi* which is transmitted to man by the bite of the wood or dog tick. The insect must remain

attached to the skin for several hours. Scratching of skin contaminated by tick feces may also be responsible for the disease. Most cases in the western part of the country occur in persons over the age of 40 years; in the eastern part, infection is commonest in children less than 15 years old.

The incubation period averages about 7 days, but varies from 3 to 12 days. *The onset of the disease is abrupt.* The outstanding manifestations are chills, generalized muscle pain and tenderness in the back and legs, fever ranging between 103° to 104°, and very severe headache which may respond poorly to analgesics. Arthralgia and abdominal pain are common. Deafness often appears in the acute stage. Agitation, delirium, mental dullness, or coma may be prominent. Tachycardia and hypotension are present in severe cases. Non-productive cough occurs occasionally and may be associated with a rickettsial pneumonitis. Among other manifestations are conjunctivitis, photophobia, conjunctival and retinal hemorrhages, splenomegaly (50 per cent), and abdominal distention. In some patients the onset is mild, and the only symptoms are lethargy, anorexia, headache, and low grade fever.

An irregular, pink, macular rash appears on the wrists, ankles, palms, soles and forearms of the second to the sixth day of the disease. Within the first day it extends to the face, neck, axillae, trunk, and buttocks. After 2 to 3 days it becomes maculopapular in character. By the fourth day the lesions are petechial and coalesce to form large purpura mainly around the joints; these may slough to form ulcers. In mild cases, the eruption may remain macular.

The fever persists for from 15 to 20 days in severe cases. Marked hypotension and renal failure may develop. Hypoprothrombinemia has been observed. Severe electrolyte and water disturbances are not uncommon. Thrombosis of major vessels appears in some cases and is responsible for gangrene, particularly of the *extremities. Suppurative parotitis* or bacterial bronchopneumonia may complicate the course of the

disease. Recovery takes place in about 14 days in mild to moderately severe cases which are not treated; in those which terminate fatally, death usually occurs in the second week and is preceded by kidney failure and shock.

The white blood count is elevated. Thrombopenia may be present. Electrolyte disturbances and chemical evidence of uremia are detectable in severely ill patients.

The possibility of Rocky Mountain spotted fever should be suspected in patients with fever, severe headache, and a petechial skin eruption if they reside in an area where wood or dog ticks are common. The specific diagnosis is established by serological studies. The Weil-Felix reaction using Proteus OX-19 and OX-2 is positive. Complement-fixing antibodies for *R. rickettsi* can be demonstrated in all cases; a significant increase (4-fold) when acute and convalescent phase serums are compared is diagnostic.

The fatality rate of Rocky Mountain spotted fever is about 20 per cent, the largest number of deaths occurring in untreated patients over 40 years of age. A fatal outcome is rare in cases treated with antibiotic agents. Three drugs are effective: Aureomycin, Terramycin, and chloramphenicol. The initial dose of the first 2 agents is 25 mg. per Kg.; this is followed by 25 mg. per Kg. per day divided into 4 to 6 equal quantities. The "loading" dose of chloramphenicol is 50 mg. per Kg.; 0.5 gm. of the antibiotic is then given every 4 hours. Treatment should be continued for at least one week. Defervescence usually occurs in 2 to 3 days. In *addition to rickettsiostatic drugs, patients often require* repair of fluid and electrolyte imbalances, an adequate caloric intake, and antimicrobial agents for the management of suppurative parotitis and secondary bacterial pneumonia.

A vaccine is available for active immunization against Rocky Mountain spotted fever. It is useful primarily in laboratory workers exposed to the rickettsiae, or in people who come in frequent contact with ticks in their environment. The wearing of special protective clothing, daily inspection

attached to the skin for several hours. Scratching of skin contaminated by tick feces may also be responsible for the disease. Most cases in the western part of the country occur in persons over the age of 40 years; in the eastern part, infection is commonest in children less than 15 years old.

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The fever persists for from 15 to 20 days in severe cases. Marked hypotension and renal failure may develop. Hypoprothrombinemia has been observed. Severe electrolyte and water disturbances are not uncommon. Thrombosis of major vessels appears in some cases and is responsible for gangrene, particularly of the extremities. Suppurative parotitis or bacterial bronchopneumonia may complicate the course of the

disease. Recovery takes place in about 14 days in mild to moderately severe cases which are not treated; in those which terminate fatally, death usually occurs in the second week and is preceded by kidney failure and shock.

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A vaccine is available for active immunization against Rocky Mountain spotted fever. It is useful primarily in laboratory workers exposed to the rickettsiae, or in people who come in frequent contact with ticks in their environment. The wearing of special protective clothing, daily inspection

of the skin of the entire body, and, if the insects are discovered, taking care not to crush them when they are removed, are helpful in preventing the disease in individuals who live in tick-infested areas.

Epidemic (Louse-Borne) Typhus Fever

Typhus fever is due to *Rickettsia prowazeki.* The organisms are transmitted from man to man by the body louse; they are usually present in the louse feces and are rubbed into broken skin by scratching.

The incubation period of the disease is about one week. The onset is very similar to that of Rocky Mountain spotted fever. The manifestations are severe. Clouding of the sensorium is common; stupor and coma may develop. The skin eruption usually appears on about the 5th day of fever. It often develops first on the axillary folds and then spreads to the trunk and extremities. The lesions begin as pink, irregular macules which then become petechiae and purpura. The signs and symptoms in the acute phase, the clinical course, complications, and laboratory findings of typhus fever closely resemble those observed in Rocky Mountain spotted fever (see above). The fatality rate in untreated cases is as high as 60 per cent, death usually occurring in the second week of illness.

The Weil-Felix test—agglutination of Proteus OX19—is positive. A more accurate method of establishing the diagnosis is by titration of complement-fixing antibody; a minimum of a 4-fold increase in titer, when serums obtained in the acute and convalescent phase of the disease are compared, is significant.

The treatment for typhus fever is the same as for Rocky Mountain spotted fever. The disease can be prevented by dusting DDT on the clothing of all people living in louse-infected areas. An effective vaccine is available.

Brill's Disease

Brill's disease is the only form of typhus fever observed in the United States today. It develops without exposure to lice; there is no doubt that it represents a recrudescence of latent *Rickettsia prowazeki* infection, the organisms having lain dormant in the tissues for 20 to 40 years or, in some instances, for as long as 50 years or more. Most patients have migrated to this country from areas of eastern or southeastern Europe where louse-borne typhus is epidemic; over 90 per cent are Jews. Many have had recognized typhus fever while living in their homeland. While, in many instances, a factor which provokes the appearance of Brill's disease cannot be discovered, surgical operations of any type appear to disrupt the balance between the host and the rickettsiae which he harbors in his tissues in some cases.

The manifestations of Brill's disease are the same as those of epidemic typhus fever. Rash appears 4 to 7 days after onset of fever, is at first macular, and then becomes petechial and even purpuric. In general, Brill's disease is mild, it may be severe, however, and death may occur. Meningeal irritation is relatively common; this is accompanied by an increased number of cells and quantity of protein in the spinal fluid in some cases.

The diagnosis is suspected in any emigrant from an area of the world in which typhus fever is present who develops a syndrome which resembles this disease; it is confirmed by the demonstration of a significant titer of complement-fixing antibody for *R. prowazeki* The Weil-Felix reaction may be negative and is of little or no help.

The treatment of Brill's disease is the same as for Rocky Mountain spotted fever. *There are no preventive measures.* It has been pointed out that patients with this infection are potentially dangerous because they may be the source of an epidemic of typhus fever if they harbor lice.

CONDITIONS IN WHICH PETECHIAL AND PUPURIC ERUPTIONS ARE PRESENT

Bacteremia
- a) Meningococcal
- b) Staphylococcal
- c) Streptococcal
- d) Gonococcal

Acute and subacute bacterial endocarditis
Scarlet fever—severe toxemia
Typhus—louse-borne
Brill's disease
Murine typhus—uncommon
Leptospirosis
Rheumatic fever
Glomerulonephritis
Henoch-Schoenlein purpura
Allergic vasculitis—serum sickness—idiopathic
Polyarteritis nodosa
Scurvy
Thrombocythemia
Thrombotic thrombopenic purpura
Thrombopenia due to—
- a) Organic arsenicals
- b) Gold salts
- c) Benzene
- d) Quinidine
- e) Pertusis vaccine
- f) Snake venom
- g) Insect bites
- h) Aplastic anemia
- i) Streptomycin
- j) Chloramphenicol
- k) Sulfonamides
- l) Myelophthisic anemia
- m) Pernicious anemia
- n) Gaucher's disease
- o) Lymphoma
- p) Leukemia
- q) Disseminated lupus erythematosus
- r) Sarcoidosis
- s) Bacterial and viral infections

Systemic Infections with Isolated Ulcerative or Nodular Lesions of the Skin

ANTHRAX (*See Chapter XV*)

The commonest form of anthrax, the malignant pustule, is characterized by the development of an isolated ulcerative lesion at the site of inoculation of the organisms. Systemic manifestations are mild or even absent in many cases, however, unless bacteremia or some other complication appears. For this reason, the description of this disease has been included in the discussion of "Infections of the Skin" (Chapter XV).

TULAREMIA

Tularemia occurs throughout the United States, Canada, Alaska, Japan, and northern and eastern Europe. The causative agent is *Pasteurella tularense*, a gram negative rod with bipolar staining granules which can be cultivated in media to which cystine is added. Infection of man follows (a) contact with infected rabbits, (b) bites by deer flies, dog or wood ticks, cats, coyotes, dogs, or skunks, (c) skinning or dressing of infected animals, and (d) ingestion of contaminated meat (uncommon). Four clinical forms of the disease have been described. (1) *Ulceroglandular*. (2) *Oculoglandular*. (3) *Gastrointestinal*. (4) *Typhoidal*.

Ulceroglandular Tularemia

This is the commonest type of the disease. The incubation period averages 2 to 5 days but may be as short as 1 or as long as 10 days. The first manifestations are headache, chills, generalized aching, weakness, and fever as high as 104°. Most patients are severely ill. Within 36 to 48 hours, the site of inoculation of the organism becomes inflamed and

ender. A papule then appears and is soon capped by a esicle which pustulates and becomes necrotic. The fully leveloped lesion is an ulcer covered by a black eschar; a canty serous discharge is present. The draining lymphatics nay become painful, and subcutaneous nodules may develop long the course of the lymphatic vessels connecting the esion in the skin and the regional lymph nodes; the appearnce is similar to that of sporotrichosis (Chapter XV). The raining lymph nodes become enlarged and painful; they emain hard, or suppurate and drain. Papular, pustular, peechial, and vesicular rashes are observed on any area of he body in some cases. The spleen is enlarged in about 25 er cent of patients.

Pneumonia occurs in approximately 7 per cent of cases of lceroglandular tularemia; it is usually diffuse and is often ccompanied by pleuritic pain and pleural effusion which nay be bloody. Sputum is scant and mucoid; hemoptysis nay occur. X-ray reveals a ground-glass appearance of the nvolved areas of the lungs and enlargement of the hilar mph nodes. The fatality rate is 30 to 40 per cent in cases ith pulmonary involvement.

The white blood count is usually elevated, and there is a elative increase of neutrophiles.

The average duration of illness in untreated ulceroglandur tularemia varies from 10 to 30 days, the less severe cases ecovering in about 2 weeks. With severe infection, fever ometimes persists for as long as 3 to 4 weeks. Convalescence often prolonged for 3 to 4 months; marked asthenia is ery common in this situation. The lymph nodes may regress nd then reappear. Suppuration may not develop until 1 onth to 2 years after the onset of the disease. Relapse may ccur as late as 2 years after recovery.

The possibility of ulceroglandular tularemia should be uspected in patients with a history of exposure, fever, an lcerated skin lesion covered by a black eschar, and regional mphadenopathy. The causative organisms can be isolated

in cystine containing broth from skin and eye lesions, and from the blood in most cases. When pneumonia is present, *P. tularense* can often be recovered from the sputum. Determination of the agglutinin level should be carried out in all patients; the titer reaches a height of 1:640 to 1:5120 in the fourth to eighth week after onset of the disease.

Oculoglandular Tularemia

The oculoglandular type of tularemia results from the implantation of *P. tularense* in the conjunctival sac. Fever of varying degree and general manifestations of infection are present. The conjunctivae and eyelids are inflamed and swollen and the periorbital area reddened and edematous. Tiny yellow papules appear on the conjunctiva and soon become ulcerated. If they develop on the cornea, perforation may occur. The pre-auricular, submaxillary, and anterior cervical lymph nodes may enlarge, become painful, and suppurate and drain. Leucocytosis is usually present.

The diagnosis of this form of tularemia is established in the same manner as in the ulceroglandular type.

Typhoidal Tularemia

Tularemia may occur without a localized lesion and with no symptoms or signs suggestive of involvement of a specific organ system. The only manifestation is fever which may be of high degree. This type of disease presents itself as an obscure fever (Chapter XVII). Approximately half of the patients develop tularemic pneumonia eventually. The diagnosis of typhoidal tularemia can be established only by isolation of *P. tularense* from the blood stream or, if the patient survives, by demonstration of the development of a significant titer agglutinating antibody for the organism.

The average fatality rate of tularemia is 6 to 7 per cent, a larger number of deaths occurring with the pneumonic and typhoidal forms than with the ulceroglandular one. Pulmonary involvement it present in 60 to 70 per cent of the

tender. A papule then appears and is soon capped by a vesicle which pustulates and becomes necrotic. The fully developed lesion is an ulcer covered by a black eschar; a scanty serous discharge is present. The draining lymphatics may become painful, and subcutaneous nodules may develop along the course of the lymphatic vessels connecting the lesion in the skin and the regional lymph nodes; the appearance is similar to that of *sporotrichosis* (Chapter XV). The draining lymph nodes become enlarged and painful; they remain hard, or suppurate and drain. Papular, pustular, petechial, and vesicular rashes are observed on any area of the body in some cases. The spleen is enlarged in about 25 per cent of patients.

Pneumonia occurs in approximately 7 per cent of cases of ulceroglandular tularemia; it is usually diffuse and is often accompanied by pleuritic pain and pleural effusion which may be bloody. Sputum is scant and mucoid; hemoptysis may occur. X-ray reveals a ground-glass appearance of the involved areas of the lungs and enlargement of the hilar lymph nodes. The fatality rate is 30 to 40 per cent in cases with pulmonary involvement.

The white blood count is usually elevated, and there is a relative increase of neutrophiles.

The average duration of illness in untreated ulceroglandular tularemia varies from 10 to 30 days, the less severe cases recovering in about 2 weeks. With severe infection, fever sometimes persists for as long as 3 to 4 weeks. Convalescence is often prolonged for 3 to 4 months; marked asthenia is very common in this situation. The lymph nodes may regress and then reappear. Suppuration may not develop until 1 month to 2 years after the onset of the disease. Relapse may occur as late as 2 years after recovery.

The possibility of ulceroglandular tularemia should be suspected in patients with a history of exposure, fever, an ulcerated skin lesion covered by a black eschar, and regional lymphadenopathy. The causative organisms can be isolated

the primary skin lesion. The regional nodes of the upper extremity (axillary and epitrochlear) are the ones most commonly involved; those in the cervical triangles and inguinal region are affected less often. The lymph nodes are swollen, firm, and tender, and the skin overlying them may be inflamed. They may remain enlarged for weeks or months. Suppuration and drainage take place in about 30 per cent of cases.

The white blood count is normal or slightly elevated. Eosinophilia has been described in a few patients. Culture of the pus in the lymph nodes is sterile. Tularemia agglutinins are absent. The Frei test and heterophile agglutination reaction for infectious mononucleosis are negative.

Cat scratch disease is benign, recovery occurring in all cases without specific therapy. Among the complications which have been observed are osteolytic lesions, meningoencephalitis, pharyngeal abscess, mesenteric adenitis with severe abdominal pain, and narrowing of the trachea by enlarged peritracheal lymph nodes, all of these are rare.

A skin test is employed to establish the diagnosis, 0.1 ml. of a 1:5 dilution of sterile pus obtained from a suppurated lymph node of a proved case is injected endermally. The reaction is considered positive if an indurated papule larger than 4 mm. in diameter and surrounded by a zone of erythema at least 1 cm. in diameter appears 48 hours after inoculation A similar result is obtained, however, in 10 per cent of normal people and in 66 per cent of those with a history suggestive of cat scratch disease in the past. Thus, a positive skin reaction is of itself not diagnostic; it must be correlated with the clinical picture before it can be considered valid.

There is no specific therapy for cat scratch disease; antimicrobial agents do not appear to be of any value.

fatal cases. Treatment with streptomycin, 0.25 gm. intramuscularly every 6 hours, produces cure of all types of the infection; the fever declines to normal in 48 to 72 hours, and local lesions and lymphadenitis resolve rapidly. The drug should be given as early in the course of the disease as possible and continued for 7 days. Oxytetracycline (Terramycin) and chlortetracycline (Aureomycin) in doses of 1 to 2 gms. per day have also proved effective, but cessation of therapy is sometimes followed by relapse.

Cat Scratch Disease
(Nonbacterial Regional Lymphadenitis)

Cat scratch disease is world-wide in distribution. Although the causative agent has not been identified, it is presumed, on the basis of epidemiologic, clinical, and experimental studies, to be a virus. A cat bite or scratch is responsible for the infection in most instances. Cases have also occurred, however, after a rabbit scratch, contamination with cat urine, injury by porcupine quills, wood splinters and thorns, and handling fresh meat.

A skin lesion develops at the site of injury in more than 50 per cent of cases. It appears in 3 to 14 days and consists of a raised, red, slightly tender papule; this is soon surmounted by a vesicle which, after rupturing, is covered by a dark eschar. Multiple primary lesions are rare. Headache, general malaise, chilliness, weakness, anorexia, nausea, and abdominal pain are the common general manifestations; all are not present in every case. Fever is usually of low degree but may reach 104°; it usually persists for only a few days but is sometimes present for several weeks. Elevation of temperature is not observed in all patients. Evanescent papular, maculopapular, or erythematous rashes, which are of less than 48 hours duration, may appear. Erythema nodosum develops occasionally. Lymphadenopathy usually is apparent 7 to 21 days after injury or the development of

the primary skin lesion. The regional nodes of the upper extremity (axillary and epitrochlear) are the ones most commonly involved; those in the cervical triangles and inguinal region are affected less often. The lymph nodes are swollen, firm, and tender, and the skin overlying them may be inflamed. They may remain enlarged for weeks or months. Suppuration and drainage take place in about 30 per cent of cases.

The white blood count is normal or slightly elevated. Eosinophilia has been described in a few patients. Culture of the pus in the lymph nodes is sterile. Tularemia agglutinins are absent. The Frei test and heterophile agglutination reaction for infectious mononucleosis are negative.

Cat scratch disease is benign, recovery occurring in all cases without specific therapy. Among the complications which have been observed are osteolytic lesions, meningoencephalitis, pharyngeal abscess, mesenteric adenitis with severe abdominal pain, and narrowing of the trachea by enlarged peritracheal lymph nodes; all of these are rare.

A skin test is employed to establish the diagnosis; 0.1 ml. of a 1.5 dilution of sterile pus obtained from a suppurated lymph node of a proved case is injected endermally. The reaction is considered positive if an indurated papule larger than 4 mm in diameter and surrounded by a zone of erythema at least 1 cm. in diameter appears 48 hours after inoculation A similar result is obtained, however, in 10 per cent of normal people and in 66 per cent of those with a history suggestive of cat scratch disease in the past. Thus, a positive skin reaction is of itself not diagnostic; it must be correlated with the clinical picture before it can be considered valid.

There is no specific therapy for cat scratch disease; antimicrobial agents do not appear to be of any value.

CHAPTER XVII

FEVER OF OBSCURE ORIGIN

Febrile episodes of short duration are almost always due to infection, the etiology of which is sometimes not defined. Prolonged elevation of temperature is, however, uncommonly associated with infectious processes, but is frequently related to disease which is non-infectious in origin. It is the purpose of this chapter to discuss briefly the conditions in which fever is present for weeks or even months without evidence of a localized lesion. These are the "obscure fevers" (F. U. O.) or "pyrexias of unknown origin" (P. U. O.).

Fever which persists for 2 to 3 months or longer, especially if accompanied by weight loss, anorexia, fatiguability, anemia etc. is usually due to organic disease. It must be stressed that infection is not the only cause of an elevated

cases, the problem remains "obscure" throughout the course of disease, and may be solved only by necropsy. In others, it is resolved after weeks or months by the appearance of specific organ or tissue dysfunction which finally discloses the exact nature of the process.

Physiologic "Fever"

There are a number of physiologic causes of "elevated" temperature. These are often overlooked and patients subjected to exhaustive, time-consuming, and expensive clinical and laboratory studies which are unrewarding. It must be stressed that normal temperature is not always 98 6° (oral).

Plotting of maximal daily temperature of large numbers of people reveals a typical probability curve. "Normal" temperature in adults may be 97.6° or 99.6°; diurnal variation is the rule, the highest "normal" level being reached between 5 and 8 P.M., and the lowest some time after midnight. The fluctuations are greater in children because of the lability of the heat-regulating mechanisms.

Exercise often raises the temperature to 100.2° or 100.4°. An increase of 1° may follow a heavy meal. An elevation of the basal temperature to 99° often accompanies ovulation. Dehydration may be responsible for fever. The temperature may be as high as 103° in babies with a poor water intake or excessive fluid loss. This is observed very uncommonly in adults unless the dehydration is superimposed on some other condition with which fever is associated.

Psychogenic factors are often the cause of elevation of temperature to 100° or a little higher. A good example of this is the slight "fever" (up to 100°) observed in many patients on admission to a hospital; subsequent recordings are usually "normal." Some women have a daily oral temperature up to 99.8° to 100°; although this may be present at any time, it is most common during the last half of the menstrual cycle. This is the syndrome of "habitual oral hyperthermia." Careful study of such individuals usually reveals evidence of a psychoneurosis, most often a chronic anxiety state.

Prolonged psychogenic fever can frequently be eliminated by the administration of small doses of a sedative agent (barbiturate or opium) but will not disappear when salicylates are given, the opposite is the case when the elevation of temperature is due to an infection There are some exceptions to this phenomenon; fever secondary to brain tumors may decrease in some cases when a small quantity of opium is administered.

The physiological causes of elevation of temperature must be *seriously considered in the differential diagnosis of "obscure fever"* before the physician embarks on the long, ardu-

ous, and expensive study to which many patients are subjected without revealing the cause of the difficulty. It is well to keep in mind that prolonged "fever" is rarely due to organic disease in people who are gaining weight, feeling well, going about their usual duties, and not developing anemia or localizing signs. The best therapy in these cases is to "throw away the thermometer."

Obscure Fever Due to Infection

The most common infectious cause of prolonged "obscure" fever is tuberculosis. This may involve only a single organ such as the lung, Fallopian tubes, pericardium, mediastinal lymph nodes, etc.; it may not be detected for weeks or months because of the absence of localizing signs (Chapters VII, VIII, XII). In addition, tuberculosis may be generalized and not produce any localized manifestations from beginning to end.

Miliary (Generalized) Tuberculosis

Miliary tuberculosis is the result of hematogenous dissemination of tubercle bacilli from hilar or mediastinal lymph nodes, pulmonary lesions, or other foci. The organisms are seeded into all of the organs, the liver, spleen, lungs, bone marrow, meninges, and kidneys being the main areas of localization; the brain, pancreas, stomach, skeletal muscles, and thyroid are involved only to a small degree or are completely spared. This type of tuberculous infection occurs most frequently in children in association with the primary pulmonary complex, but is not rare in adults, especially elderly individuals who may develop it during the course of an unrelated disease.

Miliary tuberculosis may start abruptly or insidiously. When it begins suddenly, all of the features of an acute, pyogenic infection—high fever which may be "spiking," chilliness, and generalized aching—are present. When the

onset is gradual, the manifestations are those of a low grade infectious process. Localizing signs are not detected. Cough is usually absent and weeks may elapse before x-ray study reveals disseminated lesions in the lungs. The white blood count is normal, low, or elevated to 20,000 or more with a preponderance of neutrophiles; leukemoid reactions appear occasionally. Progressive microcytic, hypochromic anemia is the rule.

The disease may run its entire course without the appearance of abnormal physical findings. Evidence of involvement of various organs (lungs, kidneys, meninges, etc.) develops in some cases, however. Splenomegaly is common. The liver often becomes enlarged.

The possibility of miliary tuberculosis must be considered in every patient with obscure fever. A positive tuberculin reaction in a young child is presumptive evidence; it has little or no diagnostic significance in adults. Biopsy of the bone marrow or liver, or both, is frequently helpful in establishing the diagnosis. The tissue should be examined microscopically for tubercles; it should also be cultured and inoculated into guinea pigs.

The treatment of miliary tuberculosis involves the simultaneous administration of streptomycin (1 gm. intramuscularly daily for the first 4 months and 1 gm. twice a week thereafter) plus para-aminosalicylic acid (2.5 to 3 gms. orally 4 times a day) and isonicotinic acid hydrazide (10 mg per Kg. per day divided into 4 equal quantities). Pyrodoxine (100 mg. per day) must be given to avoid the neurologic complications produced by INH. Therapy should be continued for a minimum of one year; a longer period may be required in some cases. The outlook for full recovery has been immeasurably improved with the use of potent tuberculostatic agents. Cure takes place in most patients in whom treatment is instituted early and continued for a sufficiently long time, providing the organisms do not become drug-resistant.

Brucellosis

Brucellosis is an infection transmitted from animals to man. It is due to *Brucella melitensis, Br. suis*, or *Br. abortus*. The disease varies greatly in frequency in various parts of the United States, being most common in the West Central part of the country.

Humans acquire brucellosis by (1) contact with the secretions or excretions of infected swine, goats, cows, sheep, or horses, (2) consumption of raw milk or dairy products, and (3) accidental inoculation while working with the organisms in the laboratory. Animals may be invaded by any of the three species of *Brucella;* thus, cows and pigs may be infected by either *Br. abortus* or *Br. suis*. Meat packers, abattoir workers, farmers, veterinarians, and laboratory workers are affected most often. Dermal contact with the organisms is more important than oral ingestion. Males get brucellosis more often than females; this merely reflects a difference in the risk of exposure related to occupation. Very few children develop clinically apparent disease despite the fact that many of them are infected; 10 per cent of the youngsters in Minnesota have a positive skin test. Multiple cases are occasionally observed in a single family.

Br. melitensis produces the most severe disease; the syndrome which appears often resembles typhoid fever. *Br. suis* is also highly invasive and is responsible for necrosis and suppuration in the tissues in which it is present. Mild illness follows infection with *Br. abortus*. The incubation period varies with the species of *Brucella*, it is 10 to 56 days with melitensis, 11 to 28 with suis, and 7 to 21 days with abortus strains.

The clinical picture of brucellosis is very difficult to define because of the protean nature of the disease. It has been pointed out that "so variable are the symptoms and so uncertain is the duration and course of this fever that it is im-

possible to give a description to which all cases can be referred."

Clinical Picture of B. abortus Infection

This type of brucellosis varies from a mild and insidious disease with low grade fever to one in which high temperature, chills, and physical and mental exhaustion are outstanding. The onset may be abrupt or gradual. The symptoms, in order of frequency, are weakness, chills, night sweats, anorexia, generalized aching, headache, nervousness, backache, joint pain, insomnia, depression, pain in the back of the neck, cough, abdominal pain, constipation, diarrhea, reduced visual acuity, ocular fatigue or pain, nausea, vomiting, neuritic pain, and genitourinary disturbances. Low-grade fever and weakness may be the only complaints. It has been said that "the intensity of the complaints and the disturbed appearance of the patient are often completely out of proportion to the paucity of objective findings." This is the distinctive feature of brucellosis.

The signs of *Br. abortus* infection are, in descending order of frequency, fever (slight, high, or "spiking," but not "undulant"), splenomegaly (5 per cent), lymphadenopathy, hepatomegaly, abdominal tenderness, cardiac abnormalities, neurologic changes, spine tenderness, skin lesions (erythematous, papular, vesicular, or discrete red elevated ulcers on the arms and hands), fundoscopic changes, orchitis (5 per cent), and jaundice. It must be emphasized that many patients reveal *no abnormalities* on physical examination

The fatality rate of untreated *Br. abortus* infection is approximately 2 per cent. The illness lasts for as long as 4 to 5 years in some cases. Eighty per cent of patients recover within one year, without antimicrobial therapy.

Brucellosis Due to Br. suis

This type of infection is more severe than that due to *Br. abortus*. Suppurative complications (listed below) are more

likely to occur and a chronic state of debility develops more frequently if a correct diagnosis is not made early and effective therapy instituted promptly.

Brucellosis Due to Br. melitensis

This is the most severe type of brucellosis. It is in this form that an "undulant" fever curve is frequently observed. The patients are very ill and lose a great deal of weight. Extreme anorexia, severe prostration, shaking chills, severe headache and backache, marked splenomegaly, delirium, coma, excruciating pain due to peripheral neuritis especially of the sciatic nerve, and spondylitis leading to permanent disability are the outstanding manifestations. Symptoms and signs may persist for a long time.

Complications of Brucellosis

Neuropsychiatric—commonest with *Br. melitensis* infection. May last from a few minutes to several hours. Not always followed by residuals.
Psychoneuroses and anxiety states (common)
Encephalopathies (diffuse or localized)
Aphasia
Dysarthria
Coma
Paralyses
Cranial Nerve Palsies (N 2,6,7,8. Permanent deafness may result)
Tinnitus
Visual disorders
Paresthesias
Meningitis (acute or chronic)
Guillain-Barré syndrome
Acute psychosis

Bone and Joint Involvement

Sondylitis (common, very painful, and incapacitating)
Suppurative arthritis (hips most often)

Cardiovascular

Bacterial endocarditis
Mycotic aneurysm

Thrombophlebitis
Electrocardiographic changes

Blood (Due to hypersplenism and most frequent with *Br. melitensis* infection)
Hemolytic anemia
Thrombopenic purpura

Genito-Urinary

Tubo-ovarian abscess (rare)
No definite evidence that abortion in humans is due to brucellosis
Pregnancy accentuates severity of the disease and this causes abortion, mainly in the first trimester.
Mastitis
Orchitis
Epididymitis
Pyelonephritis
Prostatitis (rare)

Liver

Hepatitis—jaundice
Cirrhosis
Cholecystitis
Pericholecystitis
Subdiaphragmatic abscess
Hepatic abscesses

Lungs

Pneumonia (rare)
Pleural effusion
Empyema

Eye

Corneal ulceration
Retinal hemorrhage
Optic neuritis
Retinochoroiditis
Iritis
Choroiditis
Septic retinitis
Papillitis
Papilledema
Iridocyclitis
Paralysis of extra-ocular muscles

Chronic Brucellosis

The duration of brucellosis is usually 3 months or less. Cases in which manifestations persist for 3 to 12 months are classified as *subacute;* 40 per cent of patients develop this type of disease. The infection is considered chronic if it lasts longer than a year; this is true in 45 per cent of cases. Twenty per cent of patients infected with *Br. abortus* are ill longer than one year. Three types of chronic brucellosis have been described: (a) Relapsing illness, (b) localized disease such as spondylitis, meningitis, etc., and (c) cases in which there is no evidence of active infection. In the latter, the diagnosis is often very questionable. It is suggested mainly by the presence of weakness and other manifestations of a psychoneurosis. Although the skin test may be positive in these patients, this finding is not significant since it may be present in as many as 20 per cent of normal people. Determination of the serum agglutinin level for *Brucella* is also of no help because 20 per cent of healthy individuals may have titers as high as 1·80.

Laboratory studies in brucellosis usually reveal little or no anemia. The white blood count is normal or reduced; there is always a relative lymphocytosis. Atypical cells resembling those of infectious mononucleosis may be present. C-reactive protein is demonstrable in cases with bacteremia.

The diagnosis of brucellosis cannot be made clinically. It can be established only by laboratory studies; the most important ones are (a) isolation of the organisms, and (b) determination of specific agglutinin titers.

Isolation of *Brucella* from the blood, bone marrow, or liver by culture in proper media is absolute proof of the presence of brucellosis. Blood cultures may be positive in the absence of fever in some cases.

Agglutinins for the organism are demonstrable in significant titer in the serum of practically all active cases of bru-

cellosis. A level of 1:100 is presumptive evidence. A titer of 1:320 or higher is usually detectable in bacteriologically proved cases. Rarely, agglutinin cannot be demonstrated even in the presence of bacteremia. It is very important that the test be carried out with a properly standardized antigen and that it be incubated for 48 hours before it is read. Most important is the demonstration of a rising level of agglutinin when acute and convalescent phase sera are compared. Tularemia and vaccination against cholera may be accompanied by the appearance of agglutinating antibody for *Brucella;* the titers are lower, however, than when brucellosis is present.

Skin testing with Brucella antigen is of no value because many normal individuals give positive reactions. This procedure should not be carried out prior to determination of the level of agglutinating antibody since it may provoke a rise in titer.

The prognosis in brucellosis is, in general, good The majority of patients infected with *Br. abortus* recover within one year. The outlook is more serious in melitensis infections. Death may occur within 3 weeks after onset of the disease.

The simultaneous administration of 0.5 gm. of streptomycin intramuscularly twice a day and 0 5 gm. of tetracycline orally every 6 hours for 3 weeks is very effective in curing the majority of cases of brucellosis. Relapse occurs after cessation of therapy in some patients; it should be treated in the same manner as the initial episode.

There are 3 approaches to the prevention of brucellosis· (1) Pasteurization of milk, (2) eradication of animals shown by serologic tests to have brucellosis, and (3) immunization of animals with Strain 19, an attenuated organism. This strain of *Brucella* is not entirely avirulent, it has occasionally been responsible for disease in veterinarians who have administered it.

Miscellaneous Infections Causing Obscure Fever

A number of infections other than those discussed above may be responsible for obscure fever. Although they involve specific organs and tissues, localizing signs may not develop for some time and the cause of the temperature elevation is not apparent. In most instances, however, laboratory or clinical evidence indicating the nature of the process eventually appears. The diseases which must be considered include infectious mononucleosis (Chapter VI), typhoidal tularemia (Chapter XVI), typhoid fever and salmonella septicemia (Chapter IX), syphilis (Chapter XII), pericarditis and endocarditis (Chapter VIII), tuberculous and pyogenic infections of the pelvic organs in females (Chapter XII), infectious hepatitis, liver abscesses and pylephlebitis (Chapter X), periappendiceal and subdiaphragmatic abscess (Chapter IX), renal carbuncle, pyelonephritis, perinephric abscess (Chapter XI), latent bronchiectasis (Chapter VII), sinusitis (Chapter VI), infections of bone (Chapter XIV).

Obscure Fever Due to Neoplasms

Various types of tumors commonly cause obscure fever. The lymphomas are the neoplasms most often responsible for prolonged elevations of temperature; fever may be low or high grade, "spiking," sustained, or of the Pel-Ebstein type (retroperitoneal lymphomas). Tumors of the kidney, liver (primary or metastatic), gall bladder, bile ducts, and lungs are accompanied by fever in many cases. Cancers of the stomach, breast, esophagus, jejunum, colon, and rectum are less frequently associated with an elevated temperature.

Obscure Fever Due to "Collagen" Disorders

Fever may be the only presenting manifestation in the so-called "collagen" disorders. Rheumatic fever occasionally

occurs with no manifestations other than an elevated temperature; specific evidence of the disease appears eventually in most cases, however. Rheumatoid arthritis may start in atypical fashion, the only signs being fever and mild aching of the joints. The characteristic arthritis may not develop until several weeks have elapsed. Disseminated lupus erythematosus may appear without the typical rash and present itself as a problem in obscure fever; "L.E." preparations are helpful in the diagnosis of such cases. The only manifestation in the early stages of some cases of dermatomyositis and polyarteritis nodosa is an elevated temperature.

Obscure Fever Due to Disturbances in Sweating

Disorders of the skin which interfere with sweating and normal heat exchange are often responsible for elevations of body temperature, especially in hot weather and after exercise. Among the conditions of this type which are responsible for fever are hereditary ectodermal dysplasia of the anhidrotic type, sympathectomy, acquired anhidrosis, and diffuse icthyosis.

Obscure Fever Due to Blood Dyscrasias

The leukemias, agranulocytosis, aplastic anemia, and thrombopenia with hemorrhage frequently cause fever.

MISCELLANEOUS CONDITIONS PRODUCING OBSCURE FEVER

1. Amyloid disease
2. Allergic reactions of various types
3. Heart failure
4. Cirrhosis of the liver
5. Drugs
   Streptomycin
   Penicillin
   Novobiocin

Salicylates, including para-aminosalicylic acid
Sulfonamides
Atropine
Iodine preparations (taken orally)
Propylthiouracil
Dinitrophenol
Amino acid solutions (administered intravenously)

6. Idiopathic familial hyperlipemia
7. Nodular, non-suppurative panniculitis (Weber-Christian disease)
8. Ulcerative colitis (little or no diarrhea may be present early)
9. Regional enteritis
10. Sarcoidosis
11. Malaria
12. Neurogenic fever
    Brain tumors of various types may be responsible. Also occurs in severe bulbar poliomyelitis, with cerebral involvement in falciparum malaria, and in the post-encephalitic syndrome.
13. Periodic fever
    Episodes last a few hours or days and recur in cycles which occur with great regularity in 7 or multiples of 7 days. Fever of varying degree may be the only manifestation or it may be accompanied by abdominal pain, arthralgia, vomiting, neutropenia, parotitis, hematuria, paralysis, or edema. These may occur without elevation of temperature. The attacks may be repetitive for many years. The etiologic agent is unknown. There is no effective therapy.
14. Malingering
    The possibility that "fever" is due to tampering with the thermometer must be considered in patients who appear completely healthy but who have "temperatures" of 103° to 104° daily for weeks or months The means that such patients use to give the thermometer [illegible] holding it over an el[illegible] between the fingers [illegible] rectal "temperature" by massaging the thermometer between the buttocks.

Diagnostic Approach to the Study of Obscure Fever

(1) *History:* Detailed information must be obtained concerning (a) previous diseases, (b) immunizations, (c) area in which patient lives or in which he has recently been, (d) exposure to any animals or their products, (e) mode of

onset of the present illness, and (f) nature of the symptoms and signs.

(2) *Physical Examination:* This must be carried out with the greatest care. No organ which can be examined should be neglected.

(3) *"Routine" Laboratory Studies:* The blood, urine, feces, sputum, or any other secretions or excretions which are available must be examined microscopically and, if possible, chemically.

(4) *Bacteriologic Studies:* Blood cultures must be carried out in every case of fever. Stools and urine should also be studied bacteriologically. Sputum and any other available materials should be cultured. It is important to keep in mind the possibility that anaerobes, fungi, or mycobacteria may be involved and to use media appropriate for the cultivation of these organisms. Animal inoculations are indicated in special circumstances.

(5) *Serologic Tests.* The type of study performed will depend on the diagnoses being entertained.

(6) *X-ray Examination:* Study of the heart, lungs, kidneys, and gastrointestinal tract may be very helpful.

(7) *Biopsy:* This procedure is most useful in the diagnosis of lymphomas, miliary tuberculosis, brucellosis, or disseminated neoplasms. The liver, bone marrow and lymph nodes are the tissues most likely to yield diagnostic information.

(8) *Surgical Exploration:* This may be the only method of establishing the cause of an obscure fever in some cases. Examples are (a) tumors of the lung, (b) lesions of the liver and bile ducts, (c) periappendiceal or subphrenic abscess, (d) retroperitoneal lymphoma, and (e) renal or perirenal abscess.

(9) *Following the Course of the Disease:* In not a small number of cases the fever remains obscure because localizing signs and symptoms develop slowly. Repeated physical examinations, laboratory studies, and detailed inquiry into change in symptoms may give the physician the information

necessary to point his attention in a specific direction.

Obscure fever is always a difficult problem. The primary objective of the physician must be to ascertain as rapidly as possible whether the elevation of temperature is due to a treatable disease and, if so, to carry out promptly the measures indicated to control it. It is not good practice to administer various antimicrobial agents singly, in combination, or serially in the hope that the undiscovered cause of the fever will be cured; this often turns out to be more harmful than beneficial. It must always be kept in mind that there are a great many causes for fever other than infection and that, with the exception of tuberculosis, elevation of temperature which persists for 2 to 3 months or longer is usually due to some non-infectious process.

INDEX